Addressing Long-Term Use of Benzodiazepines

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Abstract

Even though several psychiatric organisations advise against the use of benzodiazepines, they are still considered as one of the major class of drugs which are continuously misused and over-prescribed. This is especially unfavourable in the older population. These concerns support strategies for deprescribing and ensuring safe and rational use.

Such a scenario brought about the research question namely: what strategies could be adopted to address misuse of benzodiazepines. The aim was to understand local trends of benzodiazepine use and propose strategies and address appropriate use of this class of drugs. The objectives of this study were to obtain evidence of status of use of benzodiazepines and to develop frameworks which support prescribers, pharmacists and patients in addressing the concerns of over-use.

The methodology was intended to identify barriers that a prescriber encounters in deprescribing processes. Data available within the National Health System on benzodiazepine usage was analysed and factors including age, gender, medication, dose and regimen were noted. A data collection tool was developed and patients visiting community pharmacies and filling benzodiazepine prescriptions were interviewed on use of benzodiazepines.

A focus group made up of medical experts in the field was set-up to discuss the evidenced based data using analysed trends. Discussions were held regarding the potential irrational prescribing of benzodiazepines, the barriers prescribers face, access to the medication, and regulatory challenges.

Within the National Health System, 7,683 patients were on a long-term benzodiazepine and approximately 7 million benzodiazepine tablets were consumed per year. The most prescribed medicines were lorazepam (n=2,449,684), followed by bromazepam (n=2,004,240) and diazepam (n=1,174,912). These results were also reflected within the community pharmacies through the completion of the developed data tool. In the study population (n=113), statistical significant differences between duration of treatment were observed ($p<0.05$) for benzodiazepine prescribed, age groups, diagnosis, original prescriber, and dose, as well as diagnosis versus benzodiazepine prescribed.

The focus group panel identified patient assuming doctor's approval, patient not aware of adverse effects and alternatives, benzodiazepine are highly effective and are hard to replace, patient feels reliant and fears return of symptoms, deprescribing is time-consuming and demanding, and devolving of responsibility as the most significant enablers and barriers when deprescribing benzodiazepines. As primary dispensers, pharmacists are in the optimal role to campaign and raise awareness about the adverse effects associated with benzodiazepines.

Through the focus group meetings, information was gathered to construct and propose a plan which would serve as a guideline for prescribers to deprescribe benzodiazepines and to prescribe benzodiazepines long-term in a safer way. This plan could also serve as a guide for other healthcare workers to engage patients and support deprescribing. A multidisciplinary approach, contributes towards better implementation and outcomes.

Keywords: benzodiazepines, long-term use, misuse, multidisciplinary approach, frameworks, plan

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Table of Contents

List of Figures

List of Tables

Abbreviations

CBT	Cognitive Behavioural Therapy
CNS	Central Nervous System
FORTA	Fit fOR The Aged
FREC	Faculty Research Ethics Committee
GABA	Gamma-Aminobutyric Acid
GDR	Gradual Dose Reduction
HCP	Healthcare Professionals
MDH	Mater Dei Hospital
NHS	National Health System
OCD	Obsessive-Compulsive Disorder
POYC	Pharmacy of Your Choice
SSRI	Selective Serotonin Reuptake Inhibitors
STOPP	Screening Tool of Older Persons' potentially inappropriate Prescriptions
STOPPFrail	Screening Tool for Older Persons Prescriptions in Frail adults
TCA	Tricyclic Anti-Depressant

1. Introduction

1.1 Prescribing of Benzodiazepines

Misuse of benzodiazepines is a worldwide public health issue as various concerning consequences are associated with it (Votaw *et al*., 2019). All literature available states that a benzodiazepine should only be used for a short-term period i.e. less than 4 weeks, however, they continue to be prescribed and misused for a long period[1].

Benzodiazepines are mostly prescribed for their hypnotic and anxiolytic effects and are recommended for the shortest possible time and at the lowest possible dose. Upon initiating treatment with a benzodiazepine, clinicians and pharmacists should emphasise that the treatment is only for a brief and definite period (Champion and Kameg, 2021).

1.1.1 Benzodiazepine Use

Benzodiazepines act within the central nervous system (CNS), by selectively binding to the gamma-aminobutyric acid ($GABA_A$) receptors. GABA is the major inhibitory neurotransmitter within the CNS, therefore this prevents increased brain activity that may cause anxiety. This mechanism of action explains why benzodiazepines can be prescribed for a number of medical conditions, their properties include; induction of

[1] Medicines Complete [Internet]. The Royal Pharmaceutical Society. British National Formulary; 2018 [cited 31st May 2022]. Available from: www.new.medicinescomplete.com/#/browse/bnf

sleep, reduction of anxiety and aggression, reduction of muscle tone, anticonvulsant effect, as well as anterograde amnesia (Zhu *et al*., 2018).

1.1.1.1 Induction of sleep

Insomnia can be transient (jet-lag or shift work), short-term (emotional upset or illness) or chronic (anxiety, depression, drug abuse, dyspnoea) (Sutton, 2021). Benzodiazepines can reduce the time taken to fall asleep, as well as increase the duration of sleep. Compounds with a short duration of action, e.g. lorazepam, temazepam and lormetazepam have a lower chance of producing a hangover-effect upon wakening (Nielsen, 2017). However, on the other hand withdrawal symptoms are more commonly experienced with short-acting drugs.

Benzodiazepines with a prolonged duration of action can have a residual or hangover effect the next day. Nitrazepam and flurazepam are commonly prescribed as hypnotics. Accumulation can occur following repeated doses. If the patient is suffering from daytime anxiety, as well as insomnia, a long-acting benzodiazepine such as diazepam, can be given as a single dose at night to target both indications (Nielsen, 2017).

1.1.1.2 Reduction of anxiety and aggression

Benzodiazepines do not have anti-depressant effects but rather anxiolytic or 'taming' effects, therefore they should not be used as a sole treatment to treat chronic anxiety (Starcevic, 2014). When patients become aggressive following a dose of benzodiazepine, the likely cause is the withdrawal syndrome, which manifests more commonly with the short-acting compounds, as their action wears off rapidly. Benzodiazepines are

commonly used in acute anxiety states, prior to medical procedures or behavioural emergencies and they have the advantage of having a rapid effect (Petrovic *et al*., 2003), however they are not the appropriate choice to treat depression and chronic psychosis.

They should be used for the shortest amount of time and limited to the lowest possible dose. Long-acting benzodiazepines have a sustained duration of action and are sometimes given intravenously to treat a severe acute panic attack. Short-acting benzodiazepines are preferably used as adjunctive therapy for 2-4 weeks, with antidepressants when they are first prescribed, this prevents the initial worsening of symptoms. The recommendations is to follow-up weekly and discontinue the benzodiazepine treatment by week 4 by tapering the original dose. The adjustment of tapering amount and frequency should be dependent on individual response, this process could be patient led.

The elderly should be prescribed half the dose that is recommended for adults due to pharmacokinetic changes. They respond better to short-acting drugs such as lorazepam, than longer-acting drugs. Unless rebound anxiety is experienced, in which case a longer acting drug is preferred (Petrovic *et al*., 2003).

1.1.1.3 Reduction of muscle tone

An increase in muscle tone is common in anxiolytic states and may contribute to aches and pains. The relaxant effect of benzodiazepines through the $GABA_A$ receptor, particularly in the spinal cord, makes them clinically useful (Sigel and Ernst, 2018). Studies show that this reduction in muscle tone does not affect coordination up to a

certain point. Once an intravenous infusion or an overdose is administered, then airway obstruction may occur (Richards *et al*., 2012).

1.1.1.4 Anticonvulsant effect

All benzodiazepines are highly effective against chemically-induced convulsions, however not so effective against convulsions which are electrically-induced. Epilepsy is commonly treated with clonazepam, diazepam and lorazepam (Lagae, 2014).

1.1.1.5 Anterograde amnesia

When a patient is under the influence of benzodiazepines, the development of memory formation is prevented, this is a unique trait for this class of drugs. This is certainly an advantage for minor surgical and invasive procedures (Segura *et al*., 2021). They are well absorbed when given through the oral route. They reach peak plasma concentration within 1 hour of ingestion, bind strongly to plasma proteins and are lipophilic, meaning they gradually accumulate in fatty tissue (Vinkers *et al*., 2012). Benzodiazepines are generally classified by their duration of action as shown in Table 1.1.

Table 1.1: Classification of benzodiazepines. Pharmacokinetic profiles cited from Medicines Complete[1], accessed on 31st May 2022.

Ultra-short acting (<6 h)	**Short-acting (12-18 h)**	**Intermediate-acting (24 h)**	**Long-acting (24 - 48 h)**
Midazolam	Lorazepam	Alprazolam	Diazepam
	Temazepam	Nitrazepam	Flurazepam
	Oxazepam		Clonazepam
	Lormetazepam		Mexazolam
	Bromazepam		Clobazam

The duration of action is influenced by the pharmacokinetic behaviours observed for the different benzodiazepine classifications. For instance, diazepam and flurazepam produce an active metabolite with a long half-life, which explains why these benzodiazepines have such a long duration of action (Vinkers *et al.*, 2012). The benzodiazepines which are available orally on the Maltese islands are alprazolam, bromazepam, clobazam, clonazepam, diazepam, lorazepam, mexazolam, and nitrazepam. The indication of benzodiazepines is influenced by their length of duration of action; short-acting compounds are especially useful as hypnotics due to their

[1] Medicines Complete [Internet]. The Royal Pharmaceutical Society. British National Formulary; 2018 [cited 31st May 2022]. Available from: www.new.medicinescomplete.com/#/browse/bnf

diminished hangover effect upon awakening and the long-acting are highly effective for their anxiolytic and anti-convulsive properties (Vinkers *et al.*, 2012).

1.1.2 Benzodiazepine Concerns

After reviewing benzodiazepine use, there are benefits to the class which however in certain circumstances are not outweighed by patient risks and occurrence of adverse effects. Risks may be divided into undesirable side effects experienced during normal therapeutic use, toxic effects resulting from an acute overdose, tolerance, and dependence (Sithamparanathan *et al.*, 2012).

1.1.2.1 Side effects during therapeutic use

The primary side effects of benzodiazepines are drowsiness, amnesia, impaired coordination and confusion; this diminishes the patient's ability to perform manual skills such as driving. Long-acting compounds have a pronounced day-after impairment, especially when combined with alcohol (Seldenrijk *et al*, 2017). A paradoxical increase in aggression and hostility is sometimes observed when a patient is taking benzodiazepines. The affects can vary between excitement and talkativeness to antisocial acts and aggression. Increasing or decreasing the dose usually attenuates the impulses (Uzun *et al*., 2010).

The elderly have an increased sensitivity to potential side effects due to altered pharmacodynamic and pharmacokinetic profiles, specifically changes in distribution and elimination (Airagnes *et al*., 2016). Benzodiazepines with a long duration of action have

an increased likelihood to accumulate in the body and thus resulting in prolonged sedation. The elderly also have an increased sensitivity in the CNS receptors, for which this population requires special attention (Glass *et al*., 2005). When an older patient experiences anterograde amnesia as a side effect following treatment with a benzodiazepine, sometimes it may lead to a false diagnosis of early stages of dementia. This is more commonly observed with long-acting benzodiazepines and this cognitive impairment seems to improve upon discontinuing the treatment (Tseng *et al*., 2020), however, other studies disagree with this statement and state that this impairment is likely to persist even following withdrawal of benzodiazepines (Crowe and Stranks, 2018). The impaired coordination can be more problematic for the elderly, which increases the risk of falls and fractures. This is associated with prolonged use of this class of drugs and sudden increases in dosage (Sibille *et al*., 2022).

1.1.2.2 Acute toxicity

Benzodiazepines are considerably safe in instances when the patient tries to overdose. When compared to other classes, in higher doses, benzodiazepines cause prolonged sleep without a significant depression of respiratory and cardiovascular function. However, when combined with other CNS depressants, they can be life-threatening (Rickels and Moeller, 2019).

1.1.2.3 Tolerance and dependence

Tolerance i.e. the gradual escalation of the therapeutic dose needed to obtain the desired effect, and dependence occurs with all benzodiazepines. The degree of tolerance increases depending on the dosage regimen of the patient; the higher the

dose, the higher the incidence of tolerance (Jenkins, 2011). The risk of developing tolerance is associated with various factors; long-term use, high dose, alcohol consumption, short duration of action, high potency, personality disorders or other drug dependencies (Quagliato *et al.*, 2018). Abrupt cessation of treatment of benzodiazepines after weeks or months of treatment, can lead to a withdrawal. Symptoms of which include rebound heightened anxiety, dizziness, tremor, disturbed sleep, weight loss, tinnitus and sometimes convulsions. This withdrawal syndrome may occur immediately upon stopping the drug or it may take up to 3 weeks to develop (Soyka, 2017).

1.1.3 Benzodiazepine Use in Practice

In the local scenario, somewhat control of benzodiazepine prescribing is sought. They are classified as controlled substances and should only be dispensed against a prescription for narcotic and psychotropic drugs. Purchasing and dispensing registers are to be submitted to the Medicines Authority and should include patient details, prescription number and a running balance of benzodiazepine tablets, which should tally to the actual balances.

A drug Control Card is also issued, per patient, by the government against an application from a practitioner. These cards are used to control and monitor the amount and

frequency of narcotics and psychotropic drugs used as stipulated by the law[2]. Medical practitioners and pharmacists are bound by law to register the amount of tablets prescribed and dispensed on the control card, respectively. This Control Card is generally renewed every year, if deemed necessary.

Urgent prescriptions can also be issued when a patient is initially started on a benzodiazepine treatment or when the treatment duration is for a short period. This gives patients the opportunity to visit different prescribers and dispensaries, and abuse of this system to obtain a larger quantity of medication. When identified, these patients are reported to the health ministry and a circular is issued to notify prescribers and pharmacists.

Even though these systems are in play, misuse of benzodiazepines is still common, however, the extent of which is currently still unknown. Denying access of benzodiazepines to patients who have been on a long-term treatment, can be detrimental to the patient.

[2] Subsidiary Legislation: Internal Control of Dangerous Drugs – Article 8 [Online]. Available from: https://legislation.mt/eli/sl/101.2/eng/pdf
[Accessed 31st May 2022]

1.2 Deprescribing of Benzodiazepines

Deprescribing may be defined as the process of withdrawal of certain inappropriate therapy under direct supervision of a healthcare professional. The goal should be to manage polypharmacy as well as to improve patient safety and outcome (Reeve *et al.*, 2015). The deprescribing cycle usually follows Figure 1.1.

Figure 1.1: Deprescribing cycle

Various deprescribing tools are utilised to identify which patients to ween off this medication. Such as; American Geriatric Society (AGS 2019 Updated AGS Beers Criteria, 2019), Bruyère research institute deprescribing guidelines (Pottie *et al.*, 2018), FORTA list (Pazan *et al.*, 2019), NO TEARS (Lewis, 2004), START-STOPP criteria (Gallagher and O'Mahony, 2008), and STOPPFrail criteria (Lavan *et al.*, 2017). These tools recommend that benzodiazepines should be avoided in the elderly, especially in patients who already have a history of dementia, delirious state of mind, or risk of falls and fractures (Ng *et*

al., 2018). Deprescribing this class of drugs can reduce the harm done to the patient, and studies have shown that after successful deprescribing, there was no improvement or worsening of sleep quality, symptoms of anxiety or depression (Paquin *et al*., 2014). Deprescribing could mean complete discontinuation of drug or dose reduction. It could also mean a switch from a long-acting benzodiazepine to a short-acting benzodiazepine to reduce the risk of falls and fractures (Rothchild *et al*., 2007). Psychiatric patients are a high-risk patient population which pose several challenges that need to be addressed to ensure safety and effective pharmaceutical care (Mamo and Azzopardi, 2016).

Table 1.2: Comparison of deprescribing tools

Deprescribing tool	Strength	Weakness	Reference
Beers criteria	Recommends avoidance of benzodiazepines when treating elderly patients for insomnia, agitation, and delirium.	Targets only geriatric patients and focuses solely on specific indications.	AGS 2019 Updated AGS Beers Criteria, 2019
Bruyère research institute	Strongly recommends tapering down dose of benzodiazepines in patients over 65 years.	Weakly recommends to taper down dose in patients under 65 years. Only refers to patients being prescribed benzodiazepines for insomnia.	Pottie *et al*., 2018
Fit fOR The Aged (FORTA) list	Recommends to omit benzodiazepines, review and find alternatives in the elderly.	Only refers to elderly patients.	Pazan *et al*., 2020
NO TEARS	Patient – centred tool; focuses on indication, open questions, tests and monitoring, evidence, guidelines, adverse events, risk reduction or prevention, simplification and switches.	Time consuming to conduct.	Lewis, 2004
STOPP tool	Identifies harm done to the elderly patient, as a result from inappropriate prescribed medication.	Refers only to the elderly population.	Gallagher and O'Mahony, 2008
STOPPFrail criteria	Takes into consideration the elderly's pharmacokinetic and pharmacodynamic changes.	Specific to frail patients.	Lavan *et al*., 2017

1.2.7 Deprescribing Challenges

There are various enablers and barriers which are identified when suggesting deprescribing of medications. Some of which include: patients assume that they have the doctor's approval to continue treatment indefinitely, the patient might not even be aware of the adverse effects or alternatives, and the patient may feel reliant and fears that stopping this medication will result in insomnia and anxiety. There is also the risk of failure in gradual dose reduction (GDR) due to personality traits, psychological factors, and the patient's sheer willingness. Another aspect is what the healthcare providers believes and support, accessibility to the extensive healthcare resources required to adhere to the deprescribing plan, access to alternate and cognitive behavioural therapy (CBT), as well as costs, both privately and publicly (Rozsnyai *et al*., 2020 ; Reeve *et al*., 2013).

Healthcare workers can be considered enablers depending on their attitude towards benzodiazepines and deprescribing; this can be demanding, uncomfortable, complex and time-consuming, which can lead to devolving of responsibility; difficulty of stopping medications which were initially prescribed by other prescribers (Djatche *et al*., 2018; Palagyi *et al*., 2016). As primary dispensers of benzodiazepines, pharmacists have a role and opportunity to raise awareness, monitor and support the patient through GDR.

1.3 Deprescribing Plans for Benzodiazepines

Empowering and educating benzodiazepine chronic users about the potential risks and benefits of withdrawing this class of drugs is the first step to initiate deprescribing. Studies show that brochures, chart reviews, pharmacist-led programs, as well as multifactorial interventions have been successful in achieving this goal. Ensuring empowerment increases the chances of success rates, and reduces any unnecessary financial burden on the healthcare system (Niznik *et al*., 2021). There are different deprescribing plans that can be implemented to reduce the use of benzodiazepines, to safeguard the patients, especially the elderly.

1.3.1. Switching to a long-acting benzodiazepine

Previous guidelines suggested that patients are first switched to an equivalent dose of a long-acting benzodiazepine, for example diazepam, to reduce the prevalence of withdrawal symptoms. Equivalent doses to diazepam can be seen in Table 1.2. This was usually done one dose at a time over about a week, preferably taken at night. The dose is then reduced by 1-2 mg every 2-4 weeks and if withdrawal symptoms occur, the dose is maintained until the symptoms lessen. The dose reduction frequency is reduced towards the end of the process; reduced by 0.5mg every 2 weeks. Then eventually completely stopped. For long-term patients, this process may take up to several months or years (Janhsen *et al*., 2015). However, Matej *et al*., 2019 as well as other studies

explain that there is no difference in outcome when substituting to a long-acting benzodiazepine such as diazepam.

Table 1.3: Equivalent doses to 5mg of diazepam. Equivalent doses cited from Medicines Complete[1], accessed on 31st May 2022.

Diazepam 5mg
Alprazolam 250mcg
Clobazam 10mg
Clonazepam 250mcg
Flurazepam 7.5-15mg
Clordiazepoxide 12.5mg
Lorazepam 0.5-1mg
Nitrazepam 5mg
Oxazepam 10mg
Temazepam 10mg

[1] Medicines Complete [Internet]. The Royal Pharmaceutical Society. British National Formulary; 2018 [cited 31st May 2022]. Available from: www.new.medicinescomplete.com/#/browse/bnf

1.3.2 Gradual dose reduction

Dose is reduced by 5-25% every week to month. Instructions can either be written or actively supervised. The patient should be monitored every 1-2 weeks during the tapering period; improvement of alertness, cognition, daytime sedation and reduction of falls should be monitored. In the case of withdrawal symptoms, the dose should be maintained for an additional 1-2 weeks and tapering of the dose should be carried out at a slower rate. The elderly have shown an equal success rate as younger patients at withdrawing a benzodiazepine using this method (de Souza Ribeiro and Schlindwein, 2021). Withdrawal symptoms can take anywhere between 6-18 months to resolve from the last benzodiazepine dose. Prescribing beta-blockers, antidepressants and antipsychotics should be avoided during this time, as these drugs tend to aggravate the symptoms of benzodiazepine withdrawal. Medication review is especially important when this class of drugs is prescribed. The patient should also be supported through counselling and open communication during and after tapering the benzodiazepine dose (Soyka, 2017).

1.4 Research Rationale and Research Question

The rationale of this research is formulated as an attempt to reduce the number of long-term benzodiazepine users. This can be achieved by proposing frameworks to support and promote deprescribing of benzodiazepines, as well as emphasising the role of

pharmacists within this niche. This brought about the research question; what strategies can be adopted to tackle the misuse of benzodiazepines?

1.5 Aims and Objectives

The aim was to understand local trends of benzodiazepine use and propose strategies to address appropriate use of this class of drugs.

The objectives were to:

- Obtain tangible evidence of the status of use of benzodiazepines by analysing data obtained from the National Health System (NHS) and from community pharmacies.
- Develop a plan on practices to deprescribe benzodiazepines and for long-term safe use.

2. Methodology

2.1 A collaborative approach to research design

This research was set up when an unmet need was collaboratively identified. The pharmacist's contribution can improve the health service being given to a patient and help bring across the message that benzodiazepines should ideally only be prescribed for a short-term treatment. The research design and methodology were collectively discussed, and a plan was devised to bridge the gap.

The initial stages of the methodology were focused on scenario analysis and identified barriers which healthcare professionals encounter when deprescribing benzodiazepines, through a literature review. Evidence supporting the hypothesis was being collected. During this stage it was noted that no data was available to identify the extent of the healthcare issue on the Maltese Islands. Therefore, this gap was addressed in the following steps.

Various consent forms were needed to be sought as a research protocol to support the research methodology used within this study, this together with the ethics application was submitted as self-assessment to the Faculty Research Ethics Committee (FREC), with reference number: FRECMDS_2021_117 (Appendix I).

2.2 Status of Use of Benzodiazepines in the NHS

The research design included gathering a data set on benzodiazepine usage from the NHS, which included all patients on the Maltese Islands who are dispensed benzodiazepines for free through the Pharmacy of Your Choice (POYC) scheme, inpatient care at Mater Dei Hospital (MDH), and psychiatric facilities such as Mount Carmel Hospital. The NHS was contacted for access to the data and consent to publish the data as findings in this study. This was granted by the data controller and the information was sent.

The NHS have provided two sets of data: one at the patient level and the other as a general population use. The population use included the consumptions trends of benzodiazepine class, entitlement cohort numbers of specific benzodiazepines, and total number of patients on a benzodiazepine through the NHS. At the patient level, the data identified the prescribed benzodiazepine, tablet burden, and entitlement history.

2.3 Data Collection Tool Development

The complied data collection tool entitled “Benzodiazepine Use in the Community” was developed with the intention of gathering information to better understand the patient’s experience (Appendix II). The English version was compiled first which was then translated to a Maltese version and back-translated to ensure repeatability and

accuracy between the different versions of the questionnaire. The original developed data collection tool consisted of demographics questions (age and gender), benzodiazepine prescribed, tablet burden, diagnosis, treatment duration and concurrent treatment.

This questionnaire was validated by two doctors, two community pharmacists and two laypeople. The tool's reliability was tested by trained interviewers who produced the same responses upon interviewing five patients. The scope behind the validation process was to ensure the appropriateness towards the intended data collection to answer the hypothesis of this research. Feedback was evaluated and incorporated when it was deemed necessary, within the final data collection questionnaire.

The final data collection tool included: demographics (age, gender and location), benzodiazepine and tablet burden, if the patient follows that prescribed dose, diagnosed condition, number of years on benzodiazepines, whether the medication was prescribed by a psychiatrist or a family doctor, last visit to original prescriber, and any concurrent psychiatric medications.

2.4 Patient Feedback from Community Pharmacy Scenario

Thirteen pharmacies were selected and originally signed consent for data to be collected, however, ultimately, data was only collected from six pharmacies. Convenience sampling was used for the selection of these pharmacies. The tool targeted

patients over 18 years of age who accessed the selected community pharmacies with prescriptions for benzodiazepines, both through the POYC scheme, as well as private use. These patients were introduced to the research through the 'information letter' and consent was sought. Participants were required to answer the validated data collection tool which was led by trained interviewers, and needed approximately 10 minutes to complete. One hundred and thirteen (n=113) patients answered the questionnaire. To ensure confidentiality, no identifying details were collected. Since dangerous drugs are mostly collected every month, data collection was carried out within a one-month period to ensure that no patient is interviewed twice. This was done to ensure anonymity and safeguard the patient participating in the study.

2.5 Focus Group

Once all data had been collected, psychiatrists from different areas of expertise were approached and an information letter was disseminated, and the participants were asked to fill in a consent form explaining what the focus group would entail and how they were expected to participate. The discussions focused on the findings of this study, and potential misuse of benzodiazepines. During these sessions the situation in Malta was discussed, as well as potential enablers and barriers prescribers and patients face with regards to this class of drugs. Misuse of benzodiazepines, specifically, the indication, prescribing of long-acting versus short-acting benzodiazepines, dose, tapering regimen, which patients should be targeted when initiating deprescribing, and the ideal scenario when prescribing benzodiazepines, were discussed.

Proposed strategies supporting prescribing and deprescribing of benzodiazepines were developed based on evidence (Markota, 2016). The strategies were then discussed and approved in order to guide prescribers on how to deprescribe, prescribe benzodiazepines for a short duration in an acute phase and to prescribe benzodiazepines long-term in the safest way possible. Discussions on how different healthcare professionals can support this plan were held.

2.6 Data Handling

Statistical analysis of this data compiled through the interview-style questionnaire was conducted using IBM SPSS® Version 28 software[3]. Parametric and non-parametric tests were conducted depending on whether the variable was a categorical or a continuous variable. The statistical tests applied to the data were discussed with the research group, as well as a statistician. Conclusions and inferences were drawn according to the p-value achieved with the intention of identifying possible associations between various factors.

[3] IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp

3. Results

3.1 National Health System Data

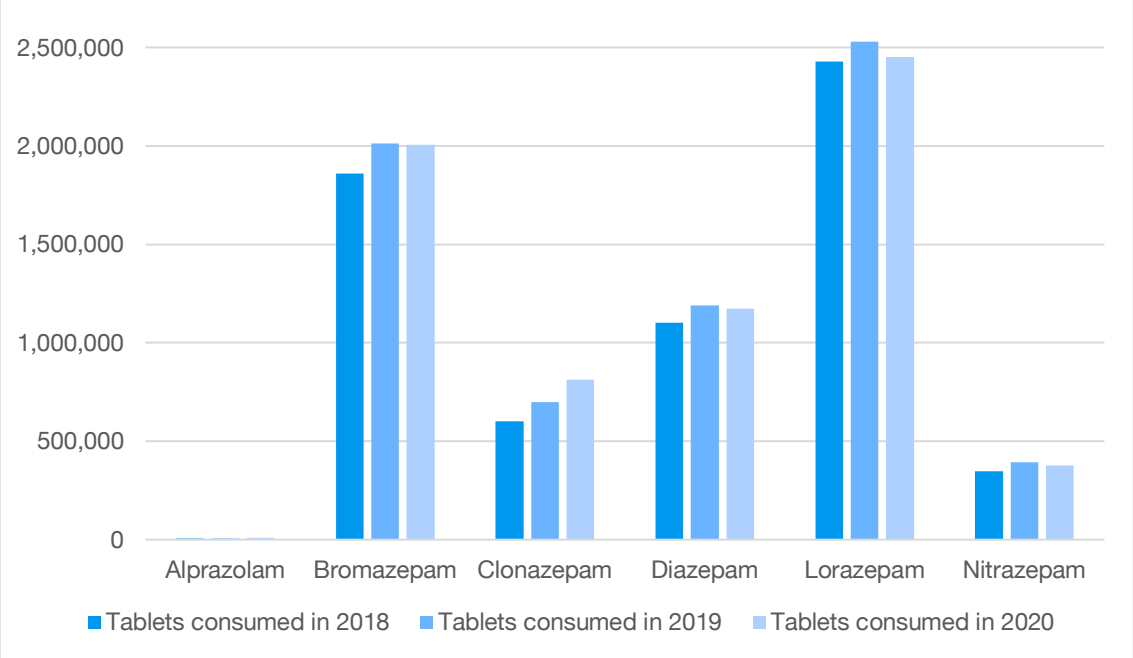
Within the NHS, 7,683 patients were found to be on long-term benzodiazepines and approximately 7 million benzodiazepine tablets were consumed per year though the NHS. The most prescribed medicine per year were lorazepam (n=2,449,684), followed by bromazepam (n= 2,004,240) and diazepam (n=1,174,912), when all doses available were combined, as show in Table 3.1.

Table 3.1: Benzodiazepine consumption trends. Data obtained from the NHS in July 2021.

Benzodiazepine	**Dose (mg)**	**Consumption in 2018**	**Consumption in 2019**	**Consumption in 2020**
Alprazolam	0.5	5,040	7,560	7,920
Bromazepam	1.5	144,000	153,000	186,000
Bromazepam	3	1,715,380	1,858,880	1,818,240
Clonazepam	0.5	340,310	418,300	469,600
Clonazepam	2	261,840	279,700	343,980
Diazepam	2	169,000	189,000	166,912
Diazepam	5	932,000	1,000,000	1,008,000
Lorazepam	1	1,785,600	1,895,600	1,896,684
Lorazepam	2	644,000	634,000	553,000
Nitrazepam	5	346,020	391,920	376,410

The consumption trend over the three years portrayed, show that there was a general increase in consumption, as depicted in Figure 3.1.

Figure 3.1: Benzodiazepine consumption trends, of all doses combined, through the NHS. Data obtained from the NHS in July 2021.



In 2021, these consumption numbers were dispensed to the stated number of patients, as shown in Table 3.2. Lorazepam was the most prescribed benzodiazepine, followed by bromazepam and diazepam.

Table 3.2: Number of patients with a Schedule V who actually received benzodiazepines through POYC. Data obtained through the NHS in July 2021.

Benzodiazepine	**Dose (mg)**	**Number of patients**
Bromazepam	1.5	431
Bromazepam	3	2,003
Bromazepam	6	124
Clobazam	10	81
Clonazepam	0.5	382
Clonazepam	2	162
Diazepam	2	380
Diazepam	5	1,033
Lorazepam	1	2,562
Lorazepam	2	639
Nitrazepam	5	539

Although these numbers are concerning, the most relevant data for the purpose of this research was the entitlement history for this class of drugs, Table 3.3.

Table 3.3: Entitlement history for each benzodiazepine. Data obtained through the NHS in July 2021.

Benzodiazepine	**Treatment duration**	**Patients**
Bromazepam	<12 months	1,558
	1-3 years	788
	4-6 years	893
	7-10 years	1,736
	>10 years	734
Clobazam	<12 months	32
	1-3 years	23
	4-6 years	23
	7-10 years	11
	>10 years	1
Clonazepam	<12 months	720
	1-3 years	372
	4-6 years	219
	7-10 years	207
	>10 years	51
Diazepam	<12 months	1,265
	1-3 years	573
	4-6 years	582
	7-10 years	993
	>10 years	366
Lorazepam	<12 months	2,599
	1-3 years	1,190
	4-6 years	1,128
	7-10 years	1,614
	>10 years	773
Nitrazepam	<12 months	425
	1-3 years	233
	4-6 years	241
	7-10 years	392
	>10 years	135

The data obtained through the NHS confirmed that the average daily dose was generally higher than what is recommended for the elderly population.

Table 3.4: Average daily dose. Data obtained through the NHS in July 2021.

Benzodiazepine	Average daily dose	Recommended daily dose in the elderly[1]
Bromazepam	8mg	3mg
Clobazam	15mg	10 – 20mg
Clonazepam	2mg	1 – 2mg
Diazepam	10mg	7.5 – 15mg
Lorazepam	3mg	0.5 – 2mg
Nitrazepam	7.5mg	2.5 – 5mg

3.2 Validation of Data Collection Tool

Through the validation process, healthcare workers suggested to include additional questions i.e. whether the patient follows the prescription or was instructed otherwise by the physician, original prescriber e.g. psychiatrist or family doctor, last visit to the original prescriber, and the locality. The laypeople who validated the questionnaire

[1] Medicines Complete [Internet]. The Royal Pharmaceutical Society. British National Formulary; 2018 [cited 31st May 2022]. Available from: www.new.medicinescomplete.com/#/browse/bnf

reworded certain questions to enable the interviewee to understand the questions being asked.

In order for the data to be more concise and efficient for the interviewer and data analysis, only psychiatric related concurrent medications were included in the data collected and any other non-psychiatric related data was discarded.

The final data collection tool included: demographics (age, gender and location), benzodiazepine and tablet burden, if the patient follows that prescribed dose, diagnosed condition, number of years on benzodiazepines, whether the medication was prescribed by a psychiatrist or a family doctor, last visit to original prescriber, and any concurrent psychiatric medications.

3.3 Data Obtained From Community Pharmacies

One hundred and thirteen patients were recruited from community pharmacies.

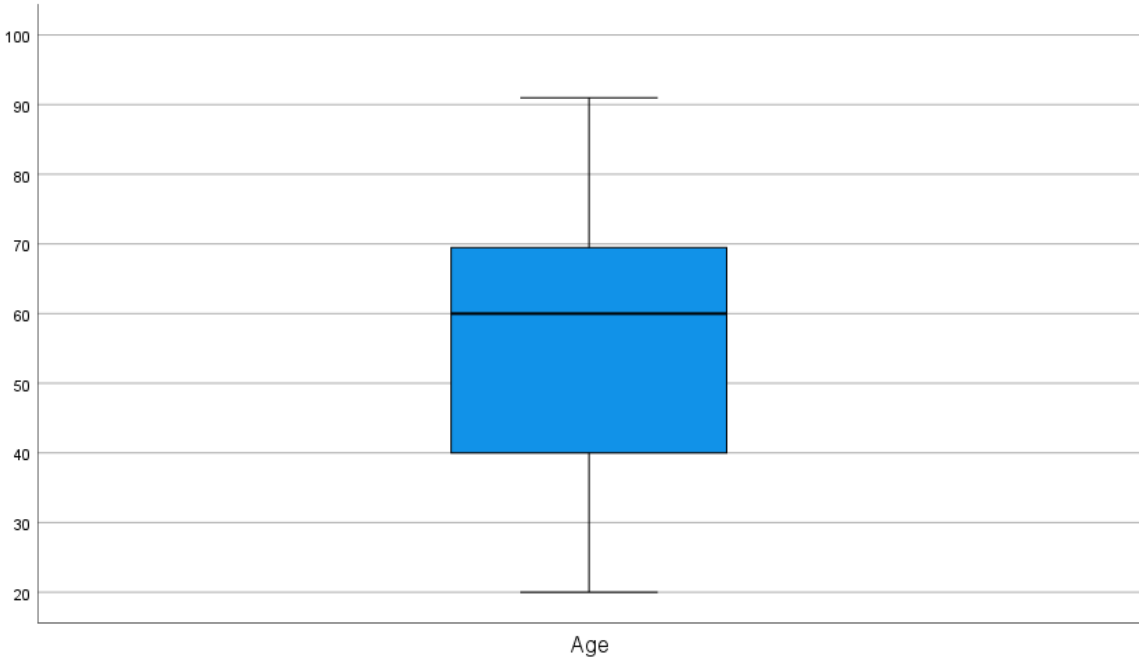
3.3.1 Demographics

The age of the participants from the questionnaire, was collected as covariate data. In order to facilitate statistical analysis, this data was transformed into a fixed factor. The box plot, as seen in Figure 3.2, indicated that the smallest value was 20, the lower

quartile was 40, the median was 60, the upper quartile was 70 and the highest value was 91.

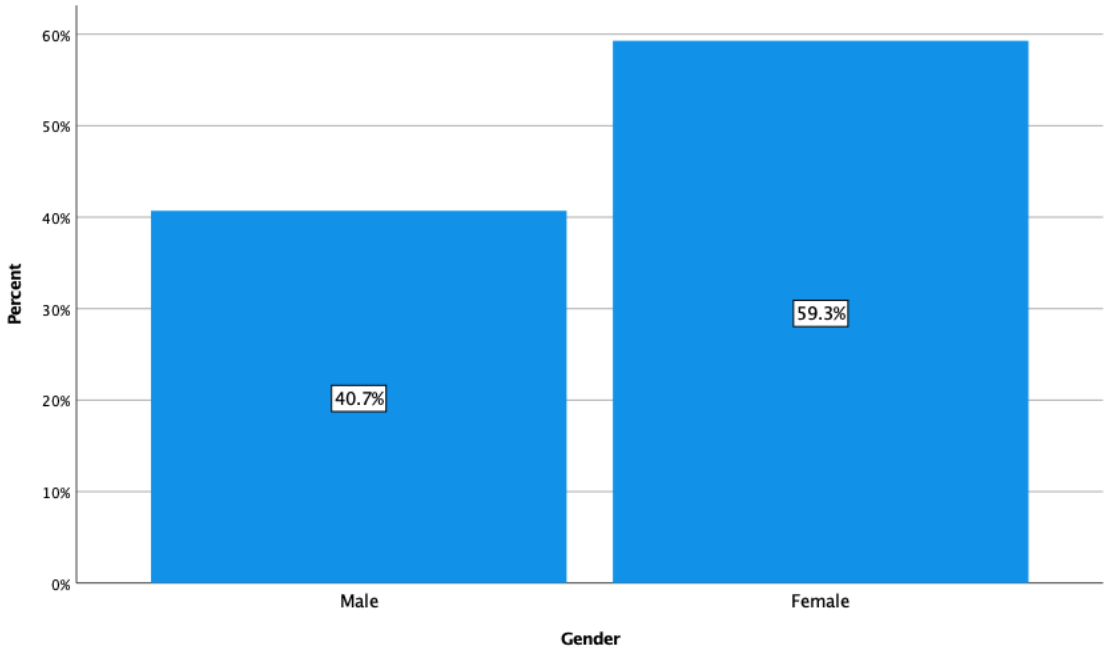
Therefore, this data was transformed into distinct levels i.e. 1 if the patient is 20-40 years, 2 if the patient is 41-60 years, 3 if the patient is 61 -70 years and 4 if the patient is more than 71 years old.

Figure 3.2: Age of the questionnaire participants (N=113)



The gender of the questionnaire participants, can be seen in Figure 3.3.

Figure 3.3: Gender of the questionnaire participants (N=113)



The pharmacies which participated in the data collection were chosen through convenient sampling. Ninety percent of the questionnaires were conducted in Zebbug, the remaining ten percent were conducted in Paola, Naxxar, Iklin, Qormi and San Gwann.

3.3.2 Descriptive statistics

Covariate data can be analysed descriptively. Within this data set, the age of the participants and the benzodiazepine tablet burden was analysed accordingly. Descriptive statistics was divided into two; measures of location and measures of dispersion. The arithmetic average i.e. mean and the median, shown in Table 3.5, reflected that the majority of the patients participating in this questionnaire were around the age of 60 and were prescribed 2 tablets daily.

The skewness of the data indicated that there were more older participants then there were younger participants, and that the tablet burden was usually lower than what they were prescribed. The kurtosis of the data indicated that the participants' age was less varied whilst the tablet burden being prescribed was more varied than the normal distribution.

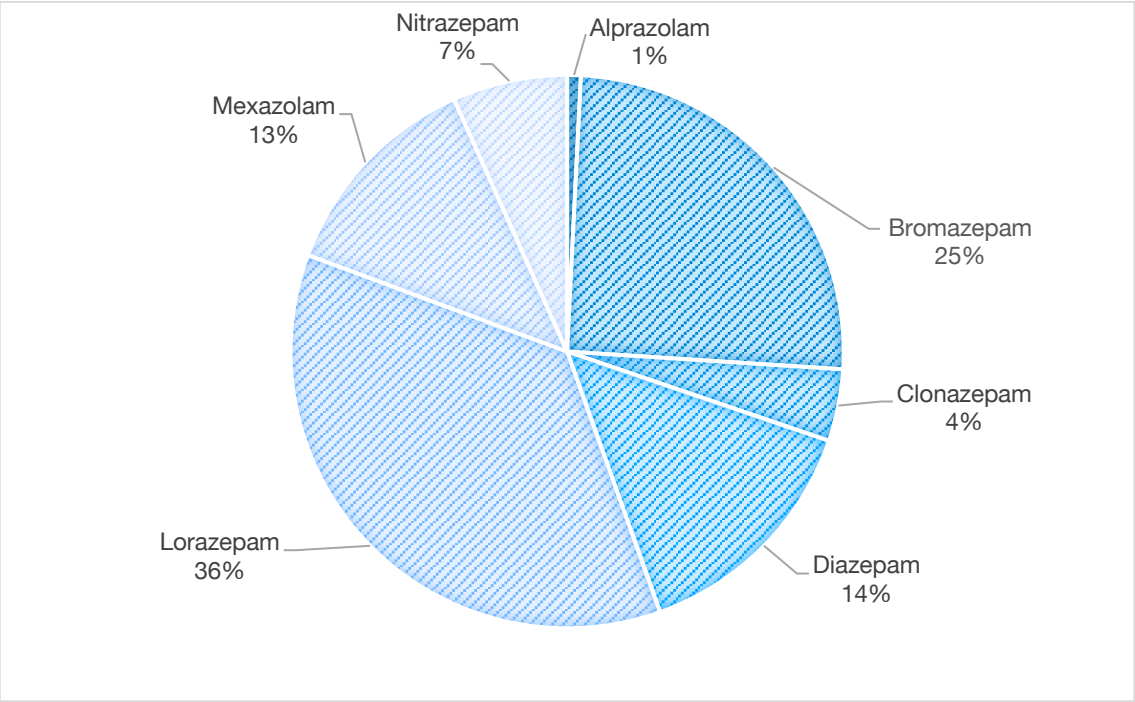
Table 3.5: Descriptive Statistics

	Age	Tablet burden
Mean	56.29	2.261
Median	60.00	2.000
Std. Deviation	18.358	1.6128
Skewness	-.252	2.513
Kurtosis	-1.021	8.985
Range	71	10.5

3.3.3 Benzodiazepines prescribed in the community

The most commonly prescribed benzodiazepine within the sample size in the community, was lorazepam, followed by bromazepam and then diazepam, as seen in Figure 3.4. This was also reflected within the data obtained from the NHS.

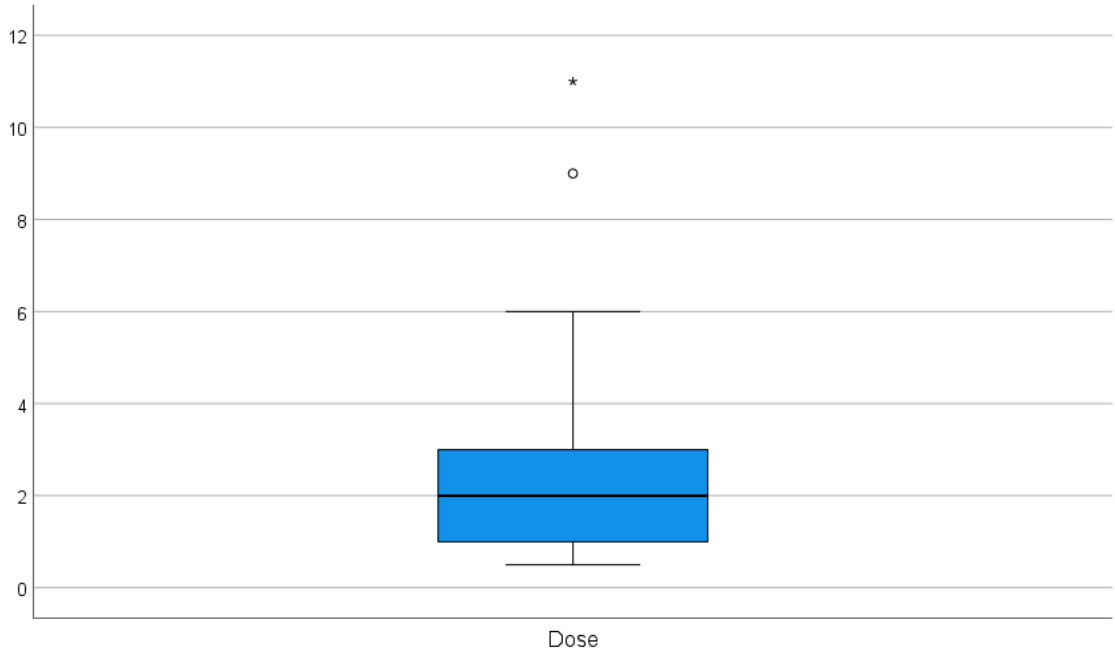
Figure 3.4: Benzodiazepines prescribed in the community (N=113)



3.3.4 Tablet burden

Figure 3.5 summarises the number of tablets prescribed within the sample size. Twenty-three percent of the participants reported that they do not follow the regimen indicated on the prescription for controlled medications, but rather have been instructed by the prescriber to take them on a 'prn' basis or at a lower dose than indicated. The prescribed dose was between 1 and 11 tablets daily, with most patients taking the medication twice daily, as seen in Figure 3.5.

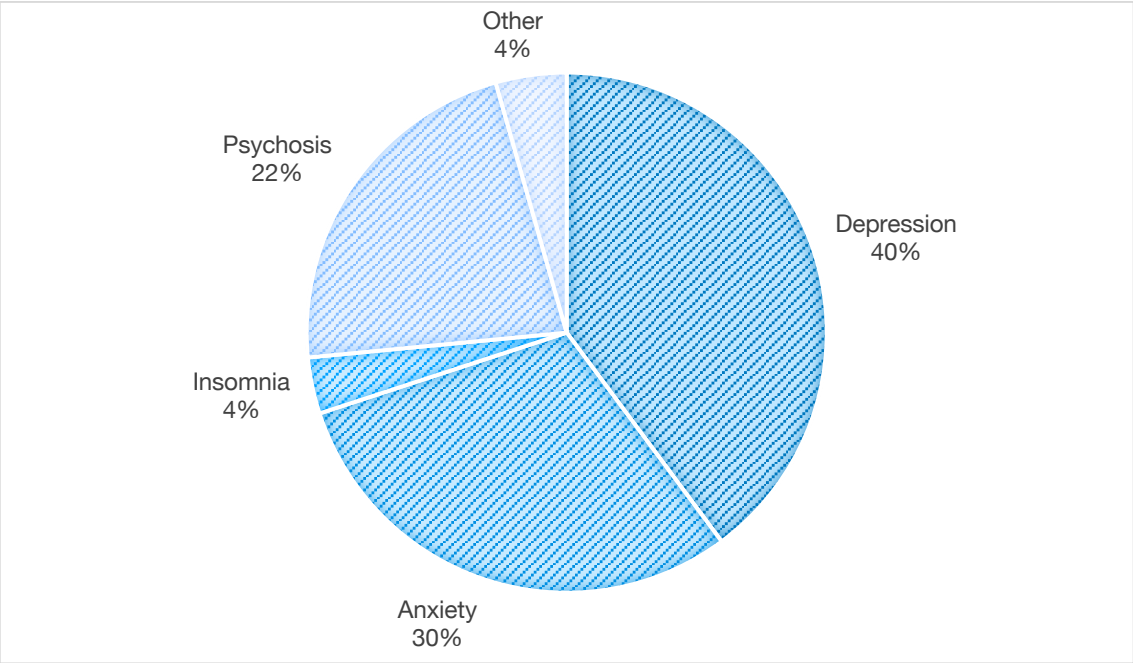
Figure 3.5: Benzodiazepine tablet burden (N=113)



3.3.5 Indication for benzodiazepine prescribed

Figure 3.6 indicated the diagnosis for which the benzodiazepine was originally prescribed. Benzodiazepines are mostly prescribed for depression, followed by anxiety, psychosis, insomnia, then other psychiatric conditions; obsessive-compulsive disorder (OCD), mood disorders, muscle pain, and stress were mentioned during data collection.

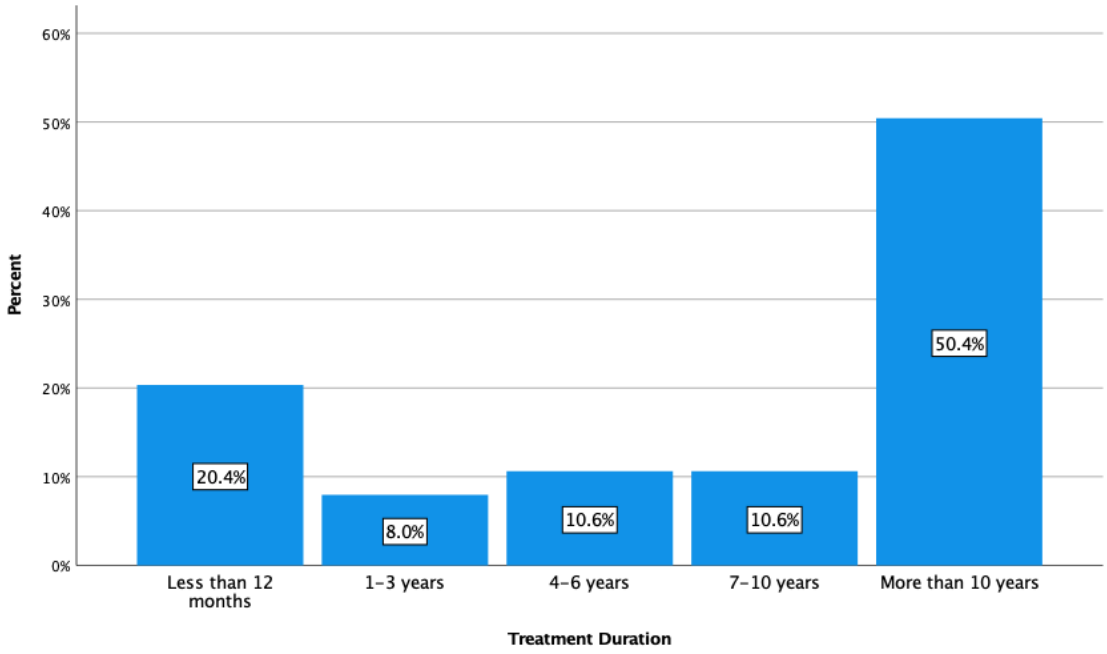
Figure 3.6: Indication for benzodiazepines prescribed (N=113)



3.3.6 Duration of treatment with benzodiazepines

Figure 3.7 shows the treatment duration for the participants in the questionnaire. Twenty percent of the participants have been taking this class of drugs as licensed, that is for a short duration of time. The remainder of the participants, almost eighty percent, have been taking this class of drugs for more than a year. This indicated that they have been prescribed benzodiazepines 'off-license'.

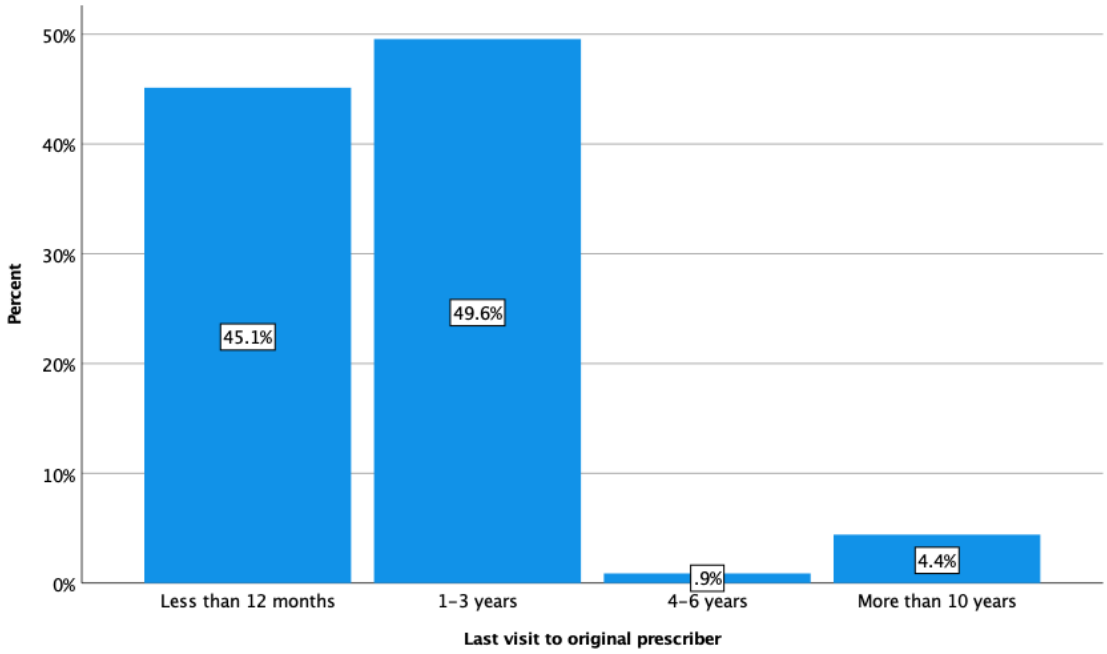
Figure 3.7: Duration of treatment of benzodiazepines (N=113)



3.3.7 Original prescriber of benzodiazepines and last visit

Seventy-seven percent of the participants' original prescriber was a psychiatrist whilst twenty-three percent of the participants' original prescriber was their family doctor. Almost all patients had visited their original prescriber in the last 3 years, as seen in Figure 3.9.

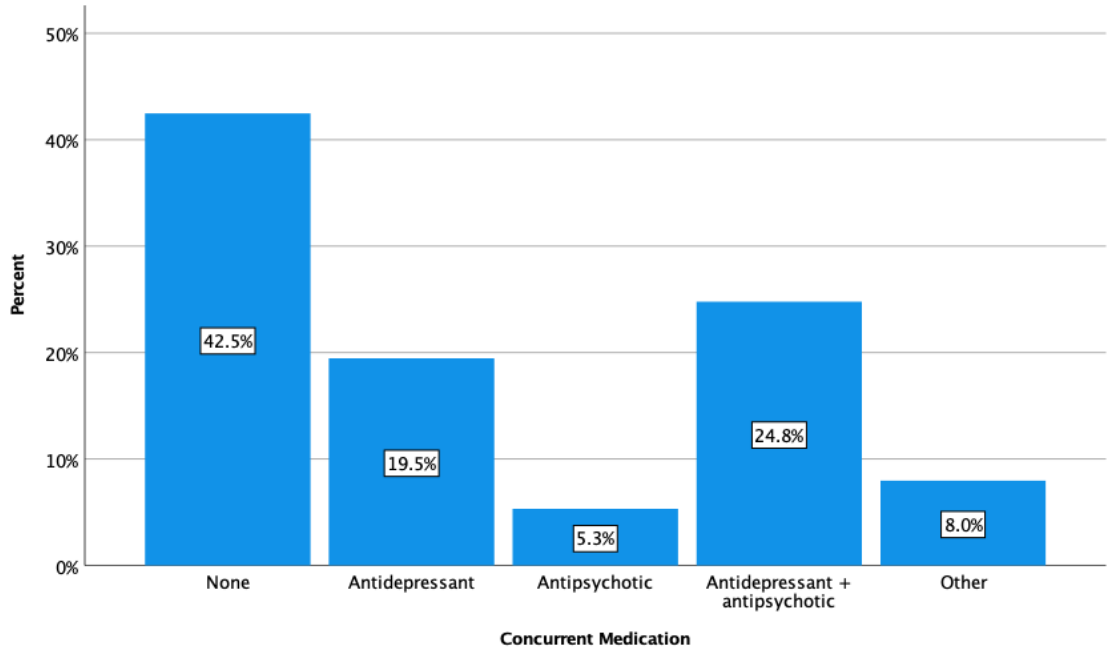
Figure 3.8: Last visit to original prescriber of benzodiazepine (N=113)



3.3.8 Concurrent psychiatric medication

Figure 3.10 shows any concurrent psychiatric medication the participants were prescribed. Other treatment included sedating antihistamine, anti-manic, CNS stimulant, and gabapentinoid medication.

Figure 3.9: Concurrent psychiatric medication (N=113)



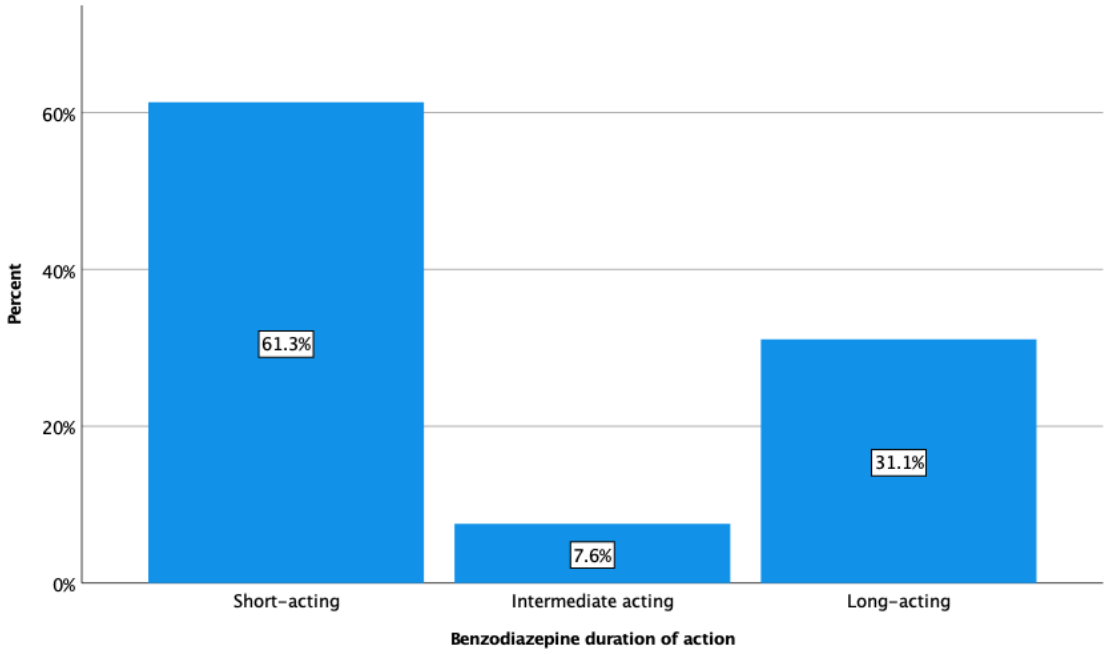
3.3.9 Urgent prescription vs control card

When participants were asked whether they own a control card or were issued an emergency prescription every time they ran out of the benzodiazepine treatment, 78% replied that they were in possession of a control card whilst the rest were issued an emergency prescription every time.

3.3.10 Benzodiazepine use according to duration of action

The benzodiazepines were split up according to their duration of action, as listed in Table 1.1. About 61% of the participants are on a short-acting benzodiazepine, 7.6% are on an intermediate-acting benzodiazepine whilst the rest are on a long-acting benzodiazepine long-term.

Figure 3.10: Benzodiazepine use according to duration of action



3.4 Statistical analysis

3.4.1 Duration of treatment vs benzodiazepine prescribed

The Chi-squared test was used to test the relationship between the two fixed factors; treatment duration with benzodiazepine and benzodiazepine prescribed, as seen in Table 3.6. This data was obtained from the questionnaire's participants.

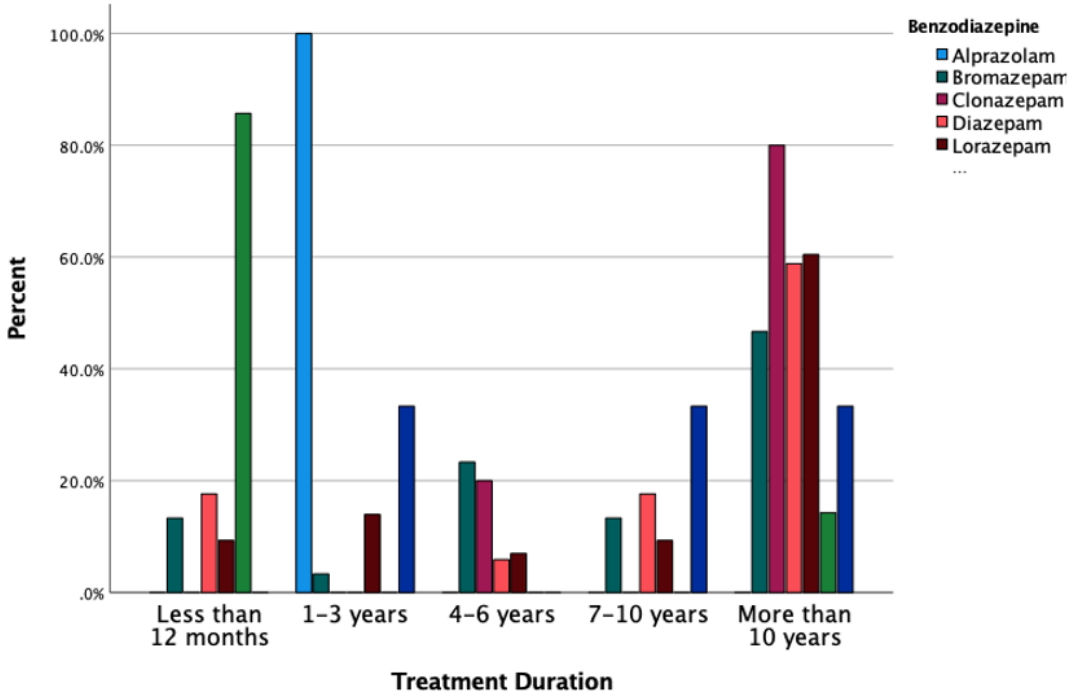
Table 3.6: Chi-squared test; treatment duration vs benzodiazepine prescribed (N=113)

		Duration					
Benzodiazepine		Less than 12 months	1-3 years	4-6 years	7-10 years	More than 10 years	Total
Alprazolam	Count	0	1	0	0	0	1
	Percentage	0.0%	11.1%	0.0%	0.0%	0.0%	0.9%
Bromazepam	Count	4	1	7	4	14	30
	Percentage	17.4%	11.1%	58.3%	33.3%	24.6%	26.5%
Clonazepam	Count	0	0	1	0	4	5
	Percentage	0.0%	0.0%	8.3%	0.0%	7.0%	4.4%
Diazepam	Count	3	0	1	3	10	17
	Percentage	13.0%	0.0%	8.3%	25.0%	17.5%	15.0%
Lorazepam	Count	4	6	3	4	26	43
	Percentage	17.4%	66.7%	25.0%	33.3%	45.6%	38.1%
Mexazolam	Count	12	0	0	0	3	15
	Percentage	52.2%	0.0%	0.0%	0.0%	5.3%	13.3%
Nitrazepam	Count	0	2	0	2	4	8
	Percentage	0.0%	22.2%	0.0%	16.7%	7.0%	7.1%
Total	Count	23	9	12	12	57	113
	Percentage	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

$X^2(24) = 71.058$, $p < 0.001$

Mexazolam was mostly observed in the short duration treatment i.e. less than 3 years – this could be since it is not available through the NHS, but is only available in the private sector. Bromazepam, clonazepam, diazepam, lorazepam and nitrazepam were mostly observed in treatment duration of more than 4 years, as seen in Figure 3.11, these are available within the NHS. There is a significant association between treatment duration and benzodiazepine prescribed ($p<0.001$).

Figure 3.11: Graphical representation of treatment duration vs benzodiazepine prescribed (N=113)



3.4.2 Duration of treatment vs age groups

The Chi-squared test was used to test the relationship between the two fixed factors; treatment duration with benzodiazepine and age group of the patients, as seen in Table 3.7. This data was obtained from the questionnaire's participants.

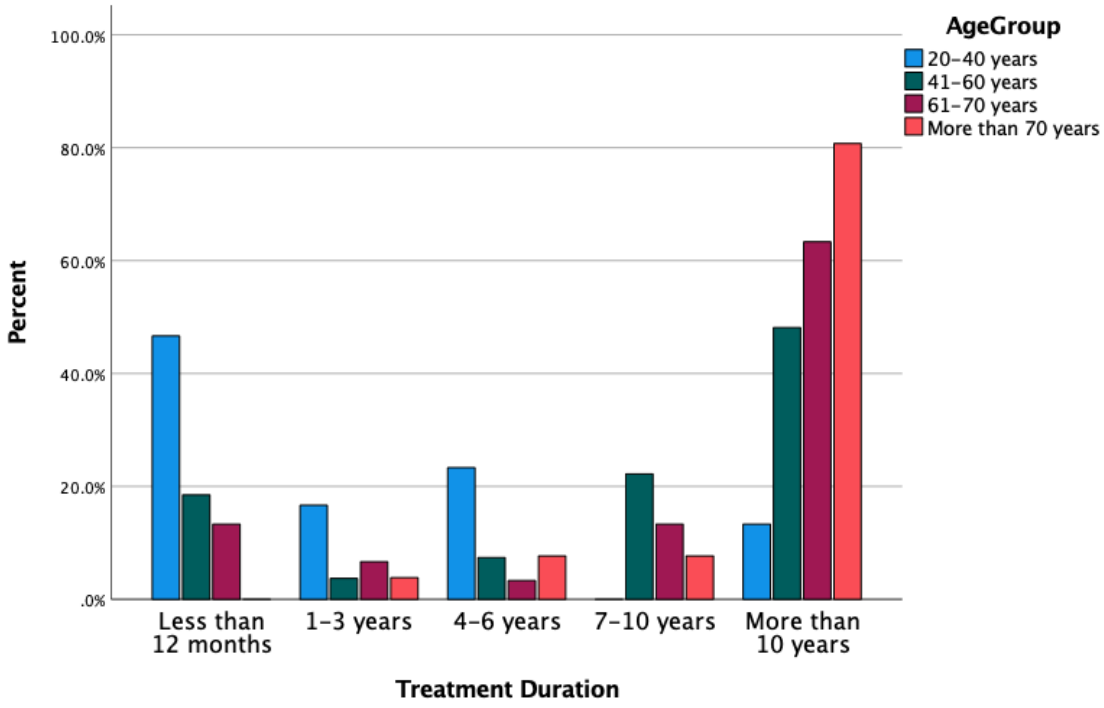
Table 3.7: Chi-squared test; treatment duration vs age groups (N=113)

		Age Group				
Treatment Duration		20-40 years	41-60 years	61-70 years	More than 70 years	Total
Less than 12 months	Count	14	5	4	0	23
	Percentage	46.7%	18.5%	13.3%	0.0%	20.4%
1-3 years	Count	5	1	2	1	9
	Percentage	16.7%	3.7%	6.7%	3.8%	8.0%
4-6 years	Count	7	2	1	2	12
	Percentage	23.3%	7.4%	3.3%	7.7%	10.6%
7-10 years	Count	0	6	4	2	12
	Percentage	0.0%	22.2%	13.3%	7.7%	10.6%
More than 10 years	Count	4	13	19	21	57
	Percentage	13.3%	48.1%	63.3%	80.8%	50.4%
Total	Count	30	27	30	26	113
	Percentage	100.0%	100.0%	100.0%	100.0%	100.0%

$X^2(12) = 47.865$, $p < 0.001$

The younger the patients were, the shorter the duration of treatment whilst the older the patients were, the longer the duration of treatment, as seen in Figure 3.12. There is a significant association between treatment duration and the age group ($p<0.001$).

Figure 3.12: Graphical representation of treatment duration vs age groups (N=113)



3.4.3 Duration of treatment vs diagnosis

The Chi-squared test was used to test the relationship between the two fixed factors; treatment duration with benzodiazepine and diagnosis, as seen in Table 3.8. This data was obtained from the questionnaire's participants.

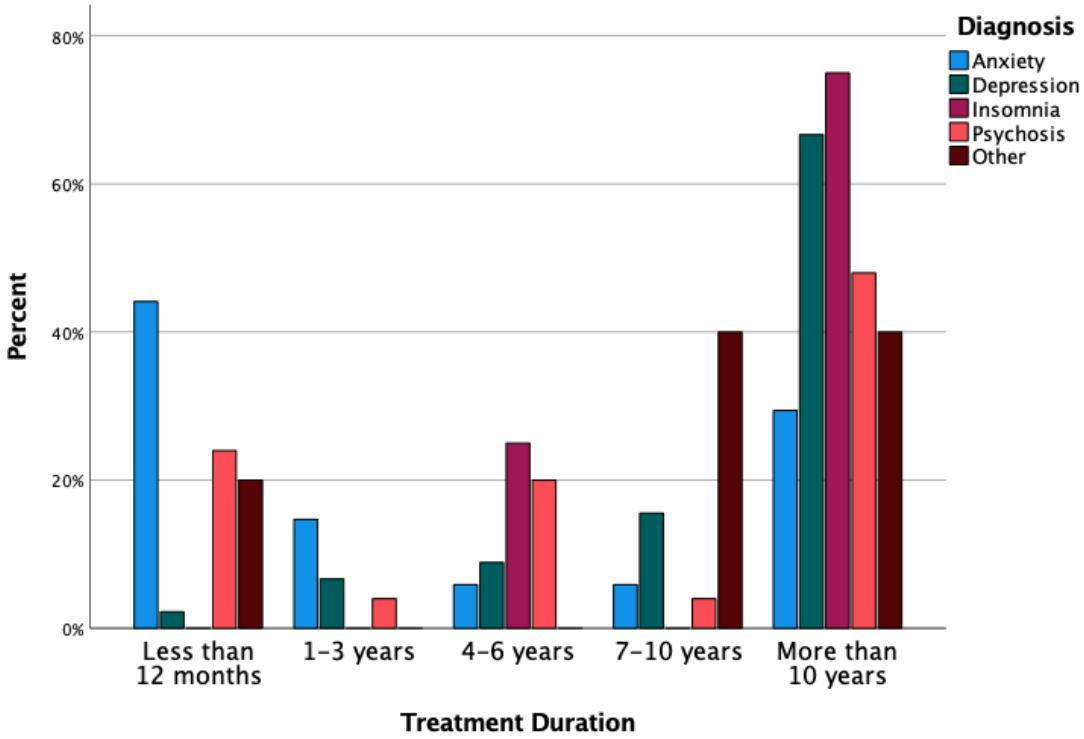
Table 3.8: Chi-squared test; treatment duration vs diagnosis (N=113)

		Diagnosis					
Treatment Duration		Anxiety	Depression	Insomnia	Psychosis	Other	Total
Less than 12 months	Count	15	1	0	6	1	23
	Percentage	44.1%	2.2%	0.0%	24.0%	20.0%	20.4%
1-3 years	Count	5	3	0	1	0	9
	Percentage	14.7%	6.7%	0.0%	4.0%	0.0%	8.0%
4-6 years	Count	2	4	1	5	0	12
	Percentage	5.9%	8.9%	25.0%	20.0%	0.0%	10.6%
7-10 years	Count	2	7	0	1	2	12
	Percentage	5.9%	15.6%	0.0%	4.0%	40.0%	10.6%
More than 10 years	Count	10	30	3	12	2	57
	Percentage	29.4%	66.7%	75.5%	48.0%	40.0%	50.4%
Total	Count	34	45	4	25	5	113
	Percentage	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

$X^2(16) = 38.368$, $p = 0.001$

The highest diagnostic count for patients who had just started treatment was anxiety, whist the highest diagnostic count for patients who had been on the treatment for more than 10 years was depression, as seen in Figure 3.13. There is a significant association between treatment duration and diagnosis (p=0.001).

Figure 3.13: Graphical representation of treatment duration vs diagnosis (N=113)



3.4.4 Duration of treatment vs the original prescriber

The Chi-squared test was used to test the relationship between the two fixed factors; treatment duration with benzodiazepine and the original prescriber, as seen in Table 3.9. This data was obtained from the questionnaire participants.

Table 3.9: Chi-squared test; treatment duration vs original prescriber (N=113)

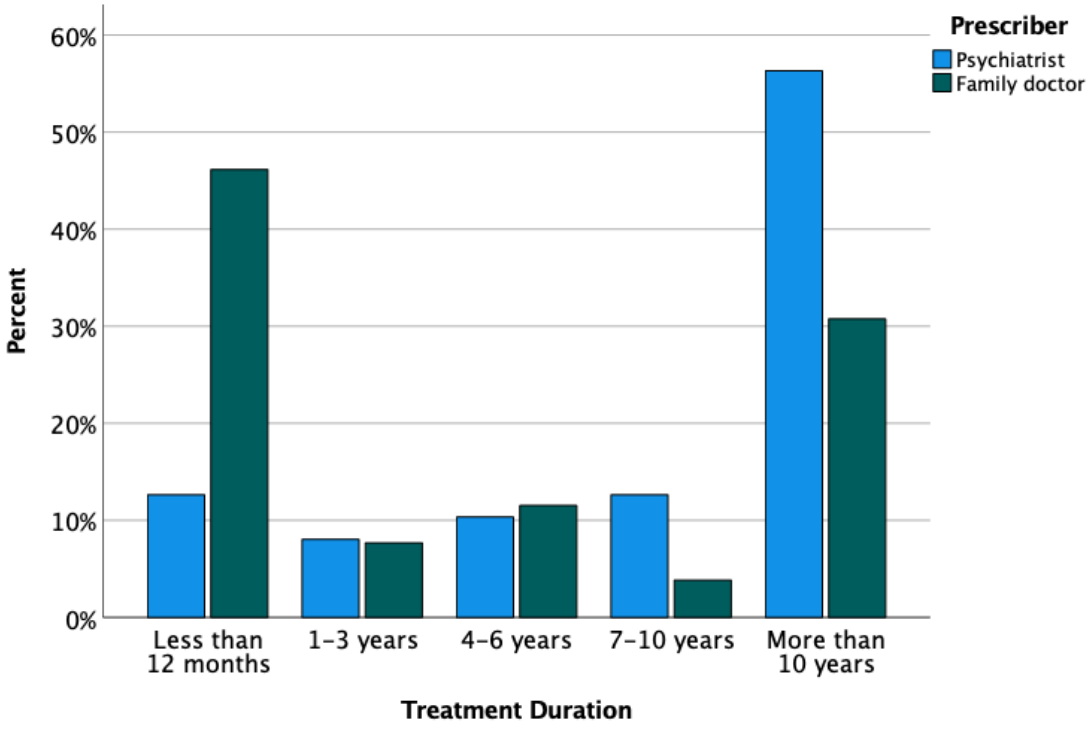
			Prescriber		
			Psychiatrist	Family doctor	Total
Treatment Duration	Less than 12 months	Count	11	12	23
		Percentage	12.6%	46.2%	20.4%
	1-3 years	Count	7	2	9
		Percentage	8.0%	7.7%	8.0%
	4-6 years	Count	9	3	12
		Percentage	10.3%	11.5%	10.6%
	7-10 years	Count	11	1	12
		Percentage	12.6%	3.8%	10.6%
	More than 10 years	Count	49	8	57
		Percentage	56.3%	30.8%	50.4%
Total		Count	87	26	113
		Percentage	100.0%	100.0%	100.0%

$X^2(4) = 15.124$, $p = 0.004$

Fifty-six percent of the participants have been on a benzodiazepine for longer than 10 years, and all of which the original prescriber was the psychiatrist. Forty-six percent of the participants have been on a benzodiazepine for less than 12 months, and the original prescriber was the family doctor, as seen in Figure 3.14. This could indicate that patients who were experiencing debilitating anxiety and depression, visited the psychiatrists as

they needed a more aggressive treatment. It must also be noted that only a psychiatrist can apply for entitlement of benzodiazepines through the NHS. There is a significant association between treatment duration and the original prescriber (p=0.004).

Figure 3.14: Graphical representation of treatment duration vs original prescriber (N=113)



3.4.5 Diagnosis vs benzodiazepine prescribed

The Chi-squared test was used to test the relationship between the two fixed factors; diagnosis and the benzodiazepine prescribed, as seen in Table 3.10. This data was obtained from the questionnaire's participants.

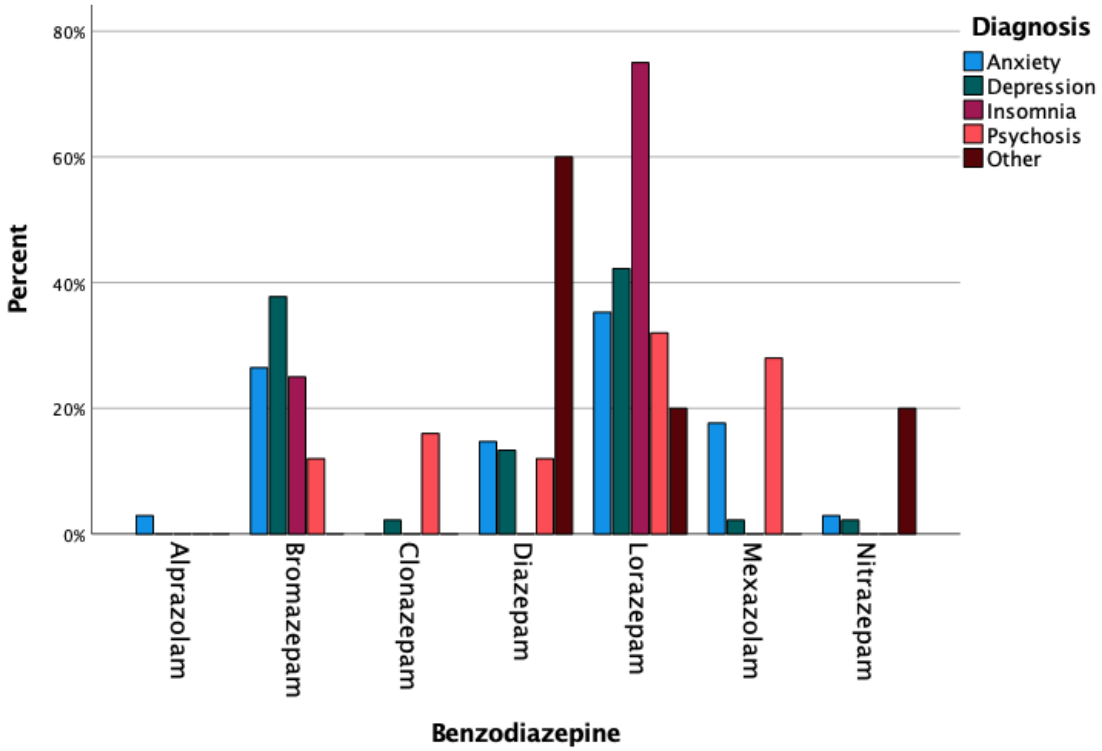
Table 3.10: Chi-squared test; diagnosis vs benzodiazepine prescribed (N=113)

		Diagnosis					
Benzodiazepine		Anxiety	Depression	Insomnia	Psychosis	Other	Total
Alprazolam	Count	1	0	0	0	0	1
	%	2.9%	0.0%	0.0%	0.0%	0.0%	0.9%
Bromazepam	Count	9	17	1	3	0	30
	%	26.5%	37.8%	25.0%	12.0%	0.0%	26.5%
Clonazepam	Count	0	1	0	4	0	5
	%	0.0%	2.2%	0.0%	16.0%	0.0%	4.4%
Diazepam	Count	5	6	0	3	3	17
	%	14.7%	13.3%	0.0%	12.0%	60.0%	15.0%
Lorazepam	Count	12	19	3	8	1	43
	%	35.3%	42.2%	75.0%	32.0%	20.0%	38.1%
Mexazolam	Count	6	1	0	7	1	15
	%	17.6%	2.2%	0.0%	28.0%	20.0%	13.3%
Nitrazepam	Count	1	5	0	1	1	8
	%	2.9%	11.1%	0.0%	4.0%	20.0%	7.1%
Total	Count	34	45	4	25	5	113
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

$X^2(24) = 39.578$, $p = 0.024$

From the data, the drugs of choice for anxiety and depression were lorazepam and bromazepam. For other psychiatric conditions, such as OCD, mood disorders, muscle pain and stress, the drug of choice was diazepam, as seen in Figure 3.15. This could be explained by the pharmacological properties of these benzodiazepines. The short-acting benzodiazepines have a good anxiolytic profile whilst longer acting benzodiazepines are more sedating, analgesic and anti-convulsant. There is a significant association between diagnosis and the benzodiazepine prescribed (p=0.024).

Figure 3.15: Graphical representation of benzodiazepine prescribed vs diagnosis (N=113)



3.4.6 Dose vs duration of treatment

The One-Way ANOVA test was used to compare mean dose between groups of patients with different treatment durations, as seen in Table 3.11.

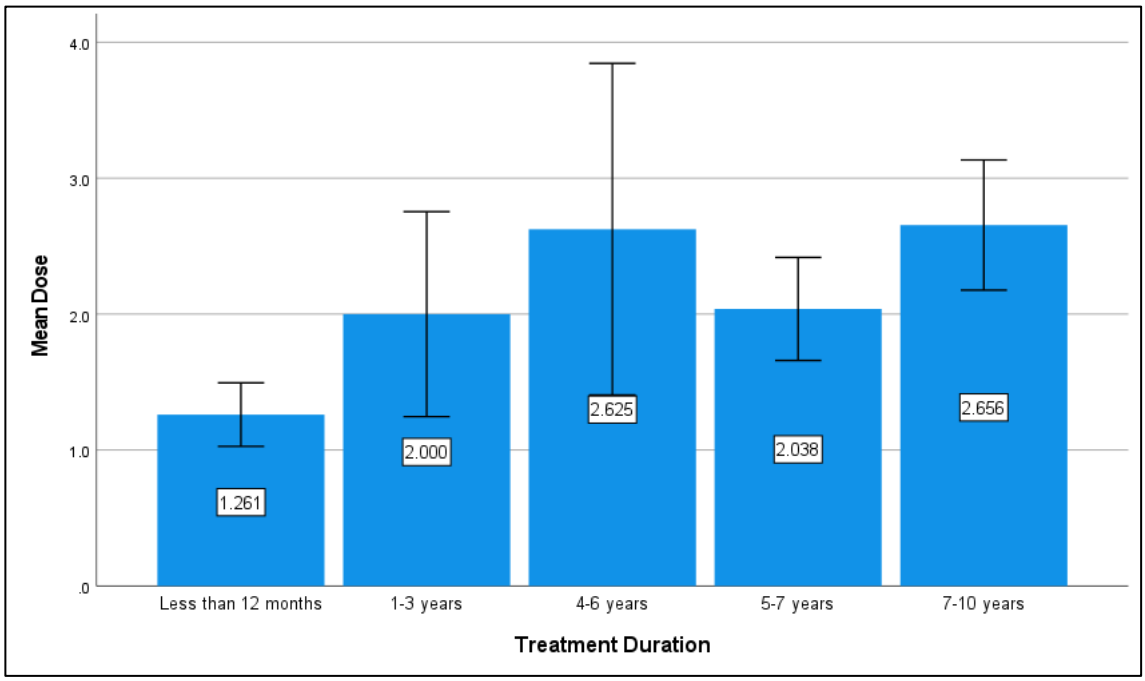
Table 3.11: One-way ANOVA test: dose vs duration of treatment (N=113)

Treatment Duration	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
				Lower Bound	Upper Bound
Less than 12 months	1.57	0.79	0.16	1.22	1.91
1-3 years	1.89	1.17	0.39	0.99	2.79
4-6 years	1.83	1.19	0.35	1.08	2.59
7-10 years	2.67	0.78	0.23	2.17	3.16
More than 7 years	3.00	0.95	0.13	2.75	3.25

$F(4, 108) = 3.665$, $p = 0.008$

Patients with longer treatment durations tend to have higher doses than patients with shorter treatment durations (p=0.008), as seen in Figure 3.16. This could indicate that the patient was experiencing tolerance, therefore a higher dose was required to achieve the same effective therapeutic response.

Figure 3.16: Graphical representation of the benzodiazepine's duration of action vs mean dose (N=113)



The error bar graph displays the 95% confidence intervals of the actual mean dose for each treatment duration group if the sample size had to be increased considerably. The two confidence intervals did not overlap indicating that their mean doses differed significantly.

3.5 Focus Group Feedback

The panel of psychiatrists who took part in the focus group sessions agreed that from their experience, benzodiazepines are mostly used in the long-term to treat generalised anxiety disorders.

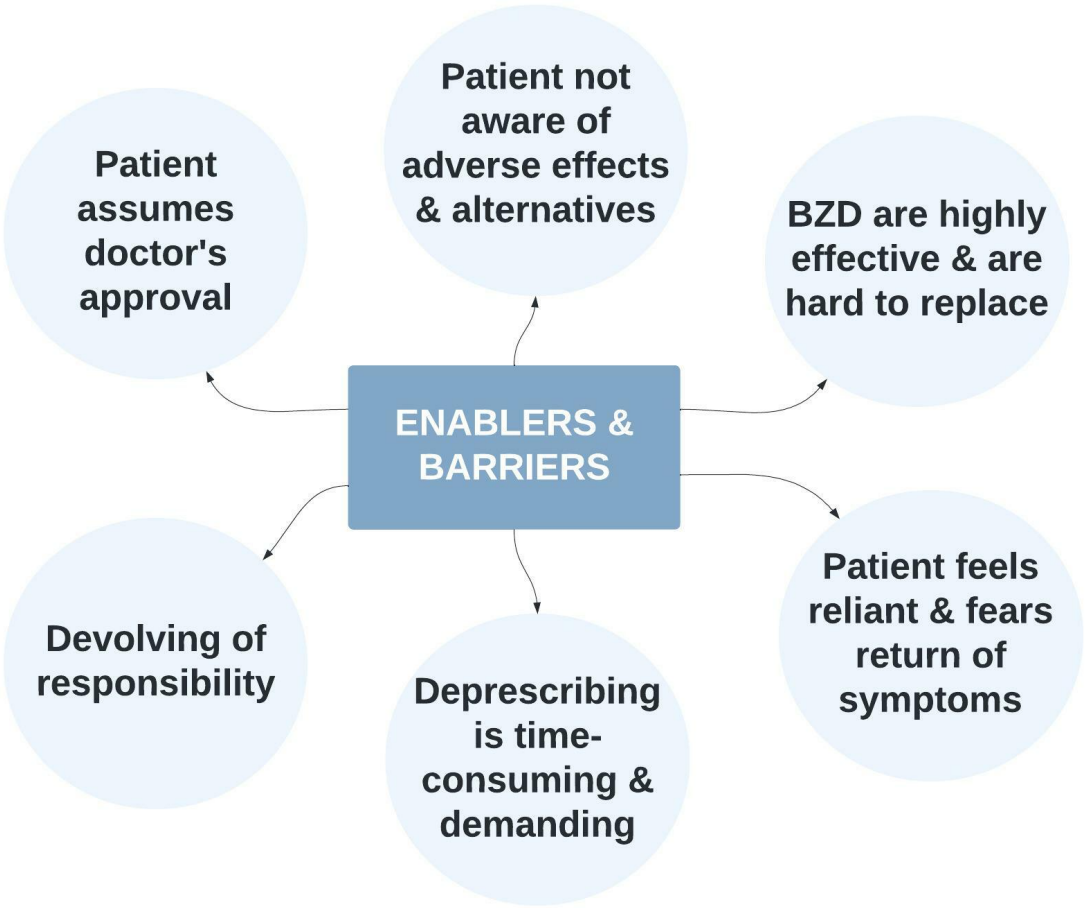
Comments were made that patients who have been on the benzodiazepine for more than 10 years were probably started on this medication due to a limited choice in the day – between a tricyclic anti-depressant (TCA) which would have taken a longer time to work and brought about various side effects and a benzodiazepine which worked instantly and brought about less side effects, in comparison to the TCA. Nowadays we have more treatment options which are recommended before prescribing benzodiazepines e.g. Selective Serotonin Reuptake Inhibitor (SSRIs).

The withdrawal syndrome is the most worrying adverse effect a patient can experience according to some participants in the focus group, however, others remarked that the falls are the most problematic adverse effect especially in the elderly; as these have a burden both on the patient as well as an economic impact on the healthcare system.

3.5.1 Enablers and barriers identified

The focus group participants rated the enablers and barriers listed in Figure 3.17 as being the most significant.

Figure 3.17: Enablers and barriers when deprescribing benzodiazepines, identified during the focus groups



These enablers and barriers were rated somewhat insignificant:

- Failure of gradual dose reduction (GDR): personality traits, psychological factors, lack of willingness.
- Healthcare providers beliefs and support, access to the healthcare resources required, access to cognitive behavioural therapy and costs.

As primary dispensers of benzodiazepines, pharmacists have a role to raise awareness, monitor and support the patient through GDR. This should be done in a sensitive manner not to alarm the patient into stopping the medication abruptly.

Some institutions believe that disseminating a leaflet highlighting the adverse effects associated with benzodiazepines is an effective way of informing and empowering the patient to take the initial step towards discontinuing benzodiazepine treatment by seeking professional advice. However, the idea of alarming these patients who have been on this treatment for years, which may lead to abrupt withdrawal of treatment, was brought up during the focus groups and it was concluded that these leaflets may after all be more harmful than beneficial. An ideal time to distribute such information would be at the very beginning when the treatment is being initiated to ensure that the patient has all the information at hand and knows that this treatment is solely temporary. Another point was brought up that when a patient is in possession of a Control Card, the patient feels entitled to the medication and continues taking the medication sometimes without a proper follow-up with the prescriber.

3.5.2 Proposal validation

The strategies proposed achieved consensus with the focus group discussion panel members. This proposal is summarised in Figure 3.18.

3.5.2.1 The ideal scenario when prescribing benzodiazepines

Suggested scenario:

i. Prescribe benzodiazepine only when the patient is functionally impaired – and only for the shortest possible period with the lowest effective dose

ii. When appropriate, simultaneously prescribe alternate treatment which takes a longer time to work

iii. Follow-up weekly and discontinue benzodiazepine by week 4 by tapering the original dose

iv. Adjust tapering amount and frequency per individual response

v. Listen, validate and support

Overall the focus groups participants agreed with this suggested scenario however they emphasised that each case is unique and should be treated as such.

3.5.2.2 Deprescribing

When discussing which factors should be considered when targeting patients for deprescribing, the elderly and patients with cognitive impairment were specifically mentioned. However, ultimately it was concluded that the prescriber should engage any and all patients on a long-term benzodiazepine, irrespective of their comorbidities.

Through the expert's experience, caregivers who attend medical follow-ups with the patient, are more inclined to take on the advice suggested by the practitioner. By comparing the benzodiazepine's cognitive impairment with that of alcohol, the caregiver can better understand the adverse effects associated with the treatment and would be more inclined to encourage the patient into the medical decision to reduce the dose or even discontinue the medication.

Another point was brought up for those patients who are still experiencing panic attacks or anxiety issues, even though they are being treated with a benzodiazepine. Emphasising that the issues were not resolved even though they have been on a benzodiazepine can be an incentive to embark on the deprescribing journey.

Suggested GDR (Pottie *et al*., 2018):

i. Reducing dose by 5-25% every week to month

ii. Instructions can either be written or supervised. Studies have supported GDR in combination with other therapies such as CBT

iii. Monitor patient every 1-2 weeks for duration of tapering. Monitoring of improvement of alertness, cognition, daytime sedation and reduction of falls. Withdrawal symptoms insomnia, anxiety, irritability, and gastro-intestinal symptoms. In the case that withdrawal symptoms occur, maintain current benzodiazepine dose for 1-2 weeks, then continue to taper at a slower rate.

During the focus groups, this GDR plan was approved. However, there was a consensus that the rate at which the benzodiazepine is reduced depends very much on the patient. Sometimes, a quicker rate of deprescribing is tolerated by the patient and sometimes it takes longer. Therefore, GDR should be treated on a case-by-case basis.

Unless withdrawal symptoms are experienced severely, usually the benzodiazepine is not switched to a long-acting benzodiazepine and the tapering of the dose is done with the original benzodiazepine prescribed. However, if withdrawal symptoms are experienced or the benzodiazepine prescribed has a very short half-life, the patient is switched to diazepam which has a long duration of action. Equivalent doses are listed in Table 1.2.

Another approach was mentioned during the focus groups, where minute changes are made to the doses e.g. reduce by 0.25mg every month, in this way developing

withdrawal symptoms is almost completely eliminated and the patient might feel more inclined to adhere to the plan. This also reduces the need to follow-up the patient frequently and can warrant a follow up after a couple of months.

3.5.2.3 Prescribing long-term benzodiazepines

Although prescribing benzodiazepines long-term is still off-license, sometimes it may be the only solution for a particular patient, or the patient experiences severe withdrawal symptoms which make it impossible to discontinue this class of drugs. Sometimes prescribers are faced with a dilemma when no other treatment manages to obtain an equivalent therapeutic efficacy.

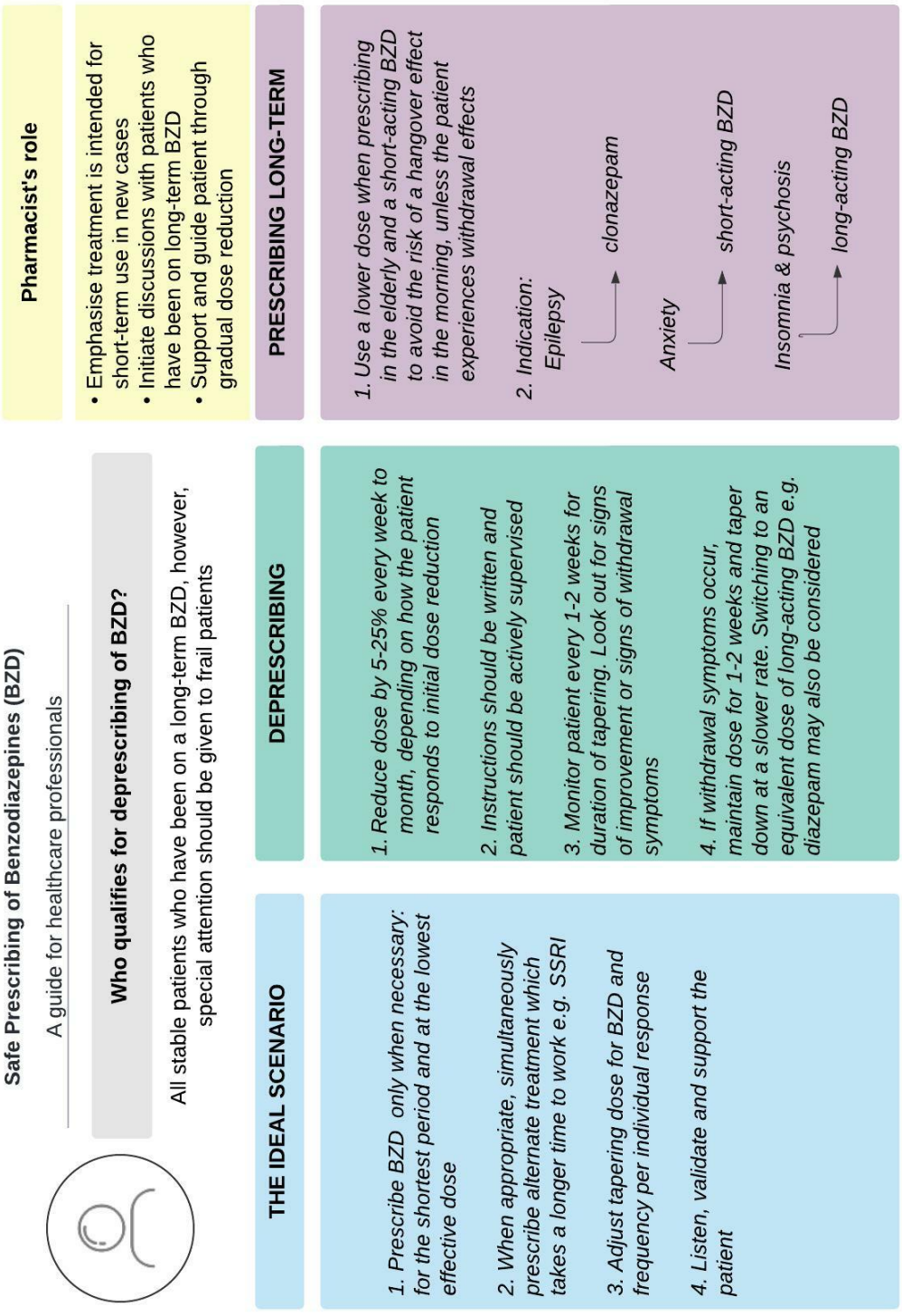
In these cases, certain aspects need to be considered;

- If the patient is elderly, the metabolism is severely reduced therefore a lower dose should be recommended for this age group. When discussions were held whether a long-acting or short-acting benzodiazepine should be prescribed, there were some issues which were discussed. Short-acting benzodiazepines bring about withdrawal symptoms whilst long-acting benzodiazepines bring about sedation and risks of falls in this fragile age group. Therefore, the choice of benzodiazepine should be on a case-by-case basis whilst considering the risks and benefits.

  The pharmacokinetic profile of this class of drugs should also be considered when prescribing them. For example, lorazepam is renally excreted and diazepam can accumulate over time, however it is easier to taper down.

- The indication or diagnosis. If the patient has been diagnosed with epilepsy, and a benzodiazepine must be prescribed, clonazepam remains the drug of choice for its anti-convulsive properties. Short-acting benzodiazepines are especially useful for their anxiolytic properties whilst long-acting benzodiazepines are especially useful for their sedating properties.

Figure 3.18: Plan proposed for safe prescribing of benzodiazepines[4]



[4] Pottie K, Thompson W, Davies S, Grenier J, Sadowski CA, Welch V *et al*. Deprescribing benzodiazepine receptor agonists: evidence-based clinical practice guideline. Canadian Family Physician. 2018;64:339-51.

4. Discussion

4.1 Current Situation of Benzodiazepine Use

This study demonstrates that there is an indication of a healthcare crisis in Malta – the long-term misuse of benzodiazepines. The most prescribed benzodiazepine over the last 3 years was lorazepam, followed by bromazepam, then diazepam. These findings were reflected both within the NHS data, as well as the community data. Therefore, the two most prescribed benzodiazepines were short-acting, whilst the third was a long-acting benzodiazepine. There was no decline in usage over the past 3 years; this poses the issues that patients were either developing tolerance and increased doses were required to achieve the same therapeutic effect or more patients were being prescribed benzodiazepines long-term through the NHS. Only 33% of the participants had been on a benzodiazepine for less than 12 months, the rest of the patients' prescriptions can all be considered off-license.

When the doses prescribed through the NHS were compared to what is usually recommended in literature[1], higher dosing regimens were observed in Malta. This could be a result of tolerance developing in the community, therefore higher doses were required to obtain the same therapeutic effect.

In the community, the data gathered suggested that there were more older patients on benzodiazepines than there were younger patients. This could be indicative that other treatment is being recommended and benzodiazepines are left as last line when alternate treatment fails, or that in the past there were limited number of options available with regards to treatment (TCA or benzodiazepine). It could also indicate that

younger patients may have been more willing to wean off the treatment and have been successful in doing so.

A discrepancy was noted between the dose prescribed versus the actual dose the patient was taking. Prescriptions were written up in this way so that the patient was able to get more medication from the pharmacy and avoided visiting the doctor for another prescription every week in the case of urgent prescriptions or every month in cases when the patient possessed a Control Card. Most of the participants were in possession of a Control Card. This means that there was the intention that the patient remains on this treatment. The Control Card ensures that the patient is collecting the benzodiazepine treatment monthly, however it cannot eliminate the possibility that the patient might be going to other prescribers and pharmacies to pick up additional doses of benzodiazepine with an urgent prescription.

Almost all patients who participated in the questionnaire have visited the original prescriber within the last 1-3 years. This may indicate that within this sample size, there no concern that the doctor might feel uncomfortable stopping a medication that another prescriber had started, as was listed as a potential barrier in the literature review. No other psychiatric medication was being prescribed to 42.5% of the participants. This brings about the queries; has the other treatment failed? Did the patient experience side effects with other treatment which resulted in deprescribing? Were the benzodiazepines prescribed first-line?

The repercussions with the 31% of patients on long-acting benzodiazepine could mean that these patients were experiencing a hangover effect in the morning, which could have led to drowsiness, falls, and overall decline in morbidity and mortality. The 61% of patients on the short-acting benzodiazepine could have experienced withdrawal symptoms as the action wore off faster.

From all the adverse effects discussed during the focus group meetings, one of the most worrying adverse effect mentioned was the withdrawal syndrome. If the patient runs out of the treatment or decides to stop the treatment abruptly for some reason or another, the patient develops the withdrawal syndrome, and these symptoms can be debilitating and could result in the patient committing suicide. The other worrying adverse effect was the risk of falls in the elderly, which effects the patient's morbidity and mortality. When the validity of enablers and barriers were discussed in the focus groups, it was agreed that being clearer with the patient when this class of medication is initiated can eliminate most of the culprits. The healthcare professionals involved must sensitively explain to the patient that this treatment is not intended for long-term use, the adverse effects associated with this medication when used long-term, and prescribe other treatment which may take a longer time to work when appropriate e.g. SSRIs and explain to the patient that they take a longer time to work and eventually they will be as therapeutically effective as the benzodiazepine. Prescribers and patients need to be encouraged to initiate the deprescribing cycle even though it is time-consuming and demanding. If the patient is uninterested in the conversation since the medication was started by a senior prescriber, the patient must be encouraged to visit that original prescriber. It should also be noted that one of the biggest barriers prescribers face is

that the medication works and sometimes there is no other treatment that compares to it therapeutically.

4.2 Clinical Considerations

The decision whether to reduce the dose or discontinue the benzodiazepine treatment, should be based on the knowledge of its effectiveness for the indication versus the risk of use. The patient's preferences play a vital role in the decision-making process. When initiating discussions with the patient about discontinuing benzodiazepines, a range of attitudes can be expected from the patient. Some may show reluctance, whilst others may show appreciation to have the opportunity to reduce the dose and stop the benzodiazepine, to minimise any potential adverse effects that may develop.

The results from this study showed that engaging the patient and explaining in a sensitive manner the risks associated with this class of drugs is of utmost importance and the way this information is communicated determines whether the tapering down of the dose or discontinuation of the treatment will be successful or not. The way in which the information is relayed to the patient, should not scare the patient into stopping the medication abruptly but needs to empower the patient to follow the deprescribing advise. When an increase in dose is necessary due to tolerance, this could be an indication that the benzodiazepine is no longer therapeutically effective. This could be used as an incentive to initiate discussions with the patient and devise a deprescribing plan.

Discussions were held to identify which inclusion criteria should be used when patients are chosen to initiate benzodiazepine deprescribing. Various factors were mentioned, such as, age, frailty, indication and cognitive function. However, ultimately, all patients who have been on a long-term benzodiazepine should be approached to initiate benzodiazepine deprescribing.

4.3 Proposed Action

Each patient on a long-term benzodiazepine should be reviewed. Other treatment options should be discussed especially if patient was started on this medication before other options were available.

Although each case is unique and should be treated as such, the following plans should serve as guidelines for prescribers[1]:

i. Prescribe benzodiazepine only when necessary, when patient is functionally impaired for the shortest possible period and with the lowest effective dose. Communicate effectively with the patient that benzodiazepines are intended for a short term only.
ii. When appropriate, simultaneously prescribe alternate treatment which takes a longer time to work e.g. SSRIs
iii. Adjust tapering dose for benzodiazepine and frequency per individual response
iv. Listen, validate, and support the patient

In the case of deprescribing (Pottie *et al.*, 2018):

i. Reducing dose by 5-25% every week to month (depending on how the patient responds to the initial dose reduction). Tapering down is done with the original benzodiazepine prescribed.

ii. Instructions should be written and may be actively supervised by other healthcare professionals (HCP) e.g. pharmacist

iii. Monitor patient every 1-2 weeks for duration of tapering. Look out for signs of improvement or signs of withdrawal symptoms. If withdrawal symptoms occur, maintain current benzodiazepine dose for an additional 1-2 weeks, and continue to taper down the dose at a slower rate.

iv. If severe withdrawal symptoms are experienced and patient is taking a short-acting benzodiazepine, he may be switched to an equivalent dose of a long-acting benzodiazepine e.g. diazepam; refer to Table 1.2 for equivalent doses.

For long-term benzodiazepine to be prescribed safely:

- Prescribing should be according to the indication; clonazepam is the drug of choice in epilepsy, short-acting benzodiazepines are the drugs of choice in anxiety and long-acting benzodiazepines are the drugs of choice in insomnia and psychosis[1] .
- Use a lower dose when prescribing in the elderly

[1] Medicines Complete [Internet]. The Royal Pharmaceutical Society. British National Formulary; 2018 [cited 31st May 2022]. Available from: www.new.medicinescomplete.com/#/browse/bnf

- In the elderly, when possible, use short-acting benzodiazepines to avoid the risk of a hangover effect in the morning, unless patient experiences withdrawal effects.

4.3.1 Contribution to the pharmaceutical service

Prior to this study, no data was available on the actual consumption and treatment duration of benzodiazepines in the Maltese Islands. The focus of this research was to explore the current situation in Malta regarding the long-term misuse of benzodiazepines and to create a plan for all healthcare professionals to improve good practice, follow up and empower the patient, encourage the prescribers to invest the time it takes to taper down the dose and discontinue the medicine. Pharmacists, being the first port of call for patients can be the catalysts in this process, to safeguard the patient from potential adverse effects from developing, with the misuse of this class of drugs. The way in which this needs to be done is of utmost importance not to alarm the patients into abruptly stopping treatments and to be guided through a tapering down process and be able to make decisions regarding their health. Having a multidisciplinary team on the same page and making the same recommendations to the patient can bring about the change that is required (Geka *et al.,*2019).

International studies have shown that pharmacist-led educational interventions have been successful in deprescribing of inappropriate medications. Martin *et al.*, 2018 explored this topic by conducting a research in which the pharmacist distributed an educational leaflet about deprescribing and engaged the prescriber by sharing evidence-

based data. The study concluded that further studies are required to be able to generalise the findings. Navy *et al.*, 2018 conducted another similar trial. In this study, a brochure was disseminated and patients on alprazolam were contacted to discuss their medication plan. This study was successful in dose reduction and deprescribing, however it concluded that alprazolam remains a challenging treatment to discontinue, due to various barriers identified.

4.4 Limitations

A major limitation was the recruitment of patients to participate in the interview-styled questionnaire as this was done by convenience sampling from selected community pharmacies. Incorporating more pharmacies into the study would have been one approach to recruit more participants and capture more data. Another limitation was the participants within the focus groups. Only psychiatrists were included in the focus group and no pharmacists and policymakers were included within the focus groups in order to obtain the perspective of other healthcare professionals and to implement the plan within the healthcare system.

Although the developed algorithm should theoretically help implement the deprescribing of benzodiazepines , it still must be proven at a practical level. Its limitations include; lack of experiences of its utility and implementation in a clinical setting, inter-rater reliability is yet to be determined, feasibility of its implementation into the community and clinical setting, and further evaluation of reliability from

different healthcare professionals working in various settings to determine if the instructions are generalisable.

4.5 Recommendations for Further Research Studies

A study could be carried out where patients are randomly selected to be part of a study; inclusion criteria being an adult, stable condition and being treated with a benzodiazepine for more than 6 weeks. An intervention is carried out by the pharmacist where the adverse effects and potential risks associated with benzodiazepines are explained to the patient in a sensitive manner. The patient should then be referred to a prescriber familiar to the patient e.g. family doctor or psychiatrist to discuss potentially deprescribing benzodiazepines. If the prescriber agrees that this is an optimal time and the patient is stable enough to start the deprescribing phase, a treatment plan is planned out and patient is followed throughout the process. The patient could check in with the pharmacist every few days to make sure that no withdrawal symptoms are being experienced. The success rate of this intervention could be calculated over several weeks to see how it impacts the community. A similar intervention could be carried out in the hospital setting e.g. rehabilitation centre, where patients can be weaned off their benzodiazepine medication once the patient is stable.

4.6 Conclusion

The plan provided within this study; a decision-support algorithm, is intended to support clinicians and pharmacists, who are crucial in engaging the patient to implement the deprescribing cycle.

In conclusion, this research has fulfilled its objectives to provide evidence of the status of use of benzodiazepines as well as to provide a plan on practices to deprescribe benzodiazepines and for long-term safer use.

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Appendix I:

Ethics Application

From: **FACULTY RESEARCH ETHICS COMMITTEE** research-ethics.ms@um.edu.mt
Subject: FRECMDS_2021_117 - ID: 8446_20042021_Yvonne Savona-Ventura
Date: 21 April 2021 at 16:02
To: yvonne.savona-ventura.14@um.edu.mt
Cc: Lilian Azzopardi lilian.m.azzopardi@um.edu.mt, Alison Anastasi alison.anastasi@um.edu.mt, Yvonne Savona Ventura yvonnesv@gmail.com

Dear Ms Yvonne Savona Ventura,

With reference to your application kindly use your UM email address when corresponding with FREC as per UREC directives.

Since your self-assessment resulted in no issues being identified, FREC will file your application for record and audit purposes but will not review it.

Any ethical and legal issues including data protection issues are your responsibility and that of your supervisor.

Kindly confirm that you sent all the documents which you attached to the UREC form together with other documents related to your study.

Kindly note that these documents are also requested for audit purposes.

L-Università ta' Malta

Ruth Stivala | Secretary
B.A.(Hons)(Melit.),M.A.(Melit.)

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https://www.um.edu.mt/ms/students/researchethics

On Tue, 20 Apr 2021 at 15:01, Yvonne Savona Ventura <yvonnesv@gmail.com> wrote:

> Good afternoon,
>
> I hope this email finds you well.
>
> Please find attached my FREC application together with the documents necessary for your consideration.
> Should you need anything else, please do not hesitate to contact me.
>
> Thank you,
> Yvonne Savona-Ventura

Patient information letter (English/Maltese]:

Dear Sir/Madam,

My name is Yvonne Savona Ventura and I am a student at the University of Malta, presently reading for a Doctorate in Pharmacy. I am conducting a research study for my dissertation titled 'Addressing Long-term use of Benzodiazepines'; this is being supervised by Prof. Lilian M Azzopardi and co-supervised by Dr Alison Anastasi. This letter is an invitation to participate in this study. Below you will find information about the study and about what your involvement would entail, should you decide to take part.

The aim of my study is to obtain tangible evidence of the status of use of benzodiazepine and to develop frameworks which support prescribers, pharmacists and patients in addressing the concerns of over-use. Your participation in this study would help contribute to a better understanding of the reality of the situation in the community regarding benzodiazepine use. Any data collected from this research will be used solely for purposes of this study.

Should you choose to participate, you will be asked to fill in a questionnaire e.g. age, gender, medication, dosage, duration of treatment, last visit to the psychiatrist, concurrent medication. Data collected will remain anonymous and the information collected will be utilized to hold focus groups.

Participation in this study is entirely voluntary; in other words, you are free to accept or refuse to participate, without needing to give a reason. You are also free to withdraw from the study at any time, without needing to provide any explanation and without any negative repercussions for you. Should you choose to withdraw, any data collected from your interview will be stored anonymously.

If you choose to participate, please note that there are no direct benefits to you. Your participation does not entail any known or anticipated risks.

Please note also that, as a participant, you have the right under the General Data Protection Regulation (GDPR) and national legislation to access, rectify and where applicable ask for the data concerning you to be erased. All data collected will be stored in an anonymised form on completion of the study.

A copy of this information sheet is being provided for you to keep and for future reference.

Thank you for your time and consideration. Should you have any questions or concerns, please do not hesitate to contact me by e-mail yvonne.savona-ventura.14@um.edu.mt; you can also contact my supervisor via email: lilian.m.azzopardi@um.edu.mt

Sincerely,

Yvonne Savona Ventura Prof. Lilian M Azzopardi

yvonne.savona-ventura.14@um.edu.mt lilian.m.azzopardi@um.edu.mt

Għażiż/a Sinjur/a,

Jiena Yvonne Savona Ventura, studenta fl-Università ta' Malta, u bħalissa qed insegwi dottorat fil-farmaċija. Ir-riċerka għad-dissertazzjoni tiegħi jisimha; *Addressing Long-term Use of Benzodiazepines*; it-tuturi tiegħi huma Prof Lilian M Azzopardi u Dr Alison Anastasi. B'din l-ittra nixtieq nistiednek tipparteċipa fir-riċerka. Hawn taħt issib aktar informazzjoni fuq l-istudju li qed nagħmel u fuq xi jkun l-involviment tiegħek jekk tiddeċiedi li tieħu sehem.

L-għan tal-istudju hu li nikseb evidenze tal-istatus tal-użu tal-*benzodiazepines* u biex niżviluppa oqfsa li jappo ġġjaw lil min jippreskrivi, lill-ispiżjara u lill-pazjenti biex jindirizzaw it-tħassib dwar l-użu żejjed ta din il mediċina. Sehmek jgħin biex ikun hawn iżjed għarfien dwar ir-realtà tas-sitwazzjoni fil-komunità rigward l-użu tal-*benzodiazepines*. L-informazzjoni kollha li tinġabar fir-riċerka tintuża biss għall-fini ta' dan l-istudju.

Jekk taqbel li tipparteċipa, tintalab timla kwestjonarju eż. età, sess, mediċina, dożaġġ, tul tat-trattament, l-aħħar żjara lill-psikjatra, mediċina oħra relatati mal- psikjatrija li tkun qed u dijanjosi. L-informazzjoni miġbura tibqa' anonima u l-informazzjoni miġbura se tintuża biex isiru *focus groups*.

Il-parteċipazzjoni tiegħek f'dan l-istudju tkun għalkollox volontarja; fi kliem ieħor, inti liberu/a li taċċetta jew tirrifjuta li tieħu sehem, mingħajr ma tagħti raġuni. Inti wkoll liberu/a li twaqqaf il-parteċipazzjoni tiegħek fl-istudju meta tixtieq, mingħajr ma jkollok

tagħti spjegazzjoni u mingħajr ebda riperkussjoni. Jekk tagħżel li tirtira mir-riċerka, l-informazzjoni li tkun laħqet ittieħdet fl-intervista miegħek titħassar dment li dan ikun teknikament possibbli (ngħidu aħna, qabel ma tiġi anonimizzata jew ippubblikata), u sakemm l-għanijiet tar-riċerka jkunu jistgħu jintlaħqu u ma jintlaqtux serjament. F'dak il-każ, l-informazzjoni tiegħek tintuża u tinżamm anonima.

Jekk tagħżel li tipparteċipa, jekk jogħġbok innota li m'hemm l-ebda benefiċċju dirett għalik. Il-parteċipazzjoni tiegħek ma fiha l-ebda riskju magħruf jew mistenni.

Bħala parteċipant/a, għandek id-dritt, skont ir-Regolament Ġenerali dwar il-Protezzjoni tad-Data (GDPR) u l-leġiżlazzjoni nazzjonali, li taċċessa, tikkoreġi u fejn hu applikabbli, titlob li l-informazzjoni li tikkonċernak titħassar. L-informazzjoni kollha li tinġabar fl-istudju tinżamm b'mod anonimu meta jintemm l-istudju.

Qed ngħaddilek kopja ta' din l-ittra biex iżżommha bħala referenza.

Grazzi tal-ħin u l-kunsiderazzjoni tiegħek. Jekk ikollok xi mistoqsija, tiddejjaqx tikkuntattjani fuq yvonne.savona-ventura.14@um.edu.mt; tista' tikkuntattja wkoll lit-tuturi tiegħi fuq: lilian.m.azzopardi@um.edu.mt

Tislijiet,

Yvonne Savona Ventura Prof Lilian M Azzopardi

yvonne.savona-ventura.14@um.edu.mt lilian.m.azzopardi@um.edu.mt

Participant's consent form (English/Maltese):

I, the undersigned, give my consent to take part in the study conducted by Yvonne Savona Ventura. This consent form specifies the terms of my participation in this research study.

1. I have been given written and/or verbal information about the purpose of the study; I have had the opportunity to ask questions and any questions that I had were answered fully and to my satisfaction.
2. I also understand that I am free to accept to participate, or to refuse or stop participation at any time without giving any reason and without any penalty. Should I choose to participate, I may choose to decline to answer any questions asked. In the event that I choose to withdraw from the study, any data collected from me will be stored anonymously.
3. I understand that I have been invited to participate in the questionnaire in which the researcher will collect data in relation to my benzodiazepine use to analyse. I am aware that the questionnaire will take approximately 10 minutes. I understand that the questionnaire is to be conducted in a place and at a time that is convenient for me.
4. I understand that my participation does not entail any known or anticipated risks.
5. I understand that there are no direct benefits to me from participating in this study. I also understand that this research may benefit others by: serving as a framework to construct a policy, to guide practitioners in the long-term use of benzodiazepines.

6. I understand that, under the General Data Protection Regulation (GDPR) and national legislation, I have the right to access, rectify, and where applicable, ask for the data concerning me to be erased.
7. I understand that all data collected will be stored anonymously on completion of the study and following publication of results.
8. I have been provided with a copy of the information letter and understand that I will also be given a copy of this consent form.
9. I am aware that focus group discussions should be considered confidential and that I should not disclose details of those participating and/or of the nature of discussions to others.

I have read and understood the above statements and agree to participate in this study.

Name of participant: _____

Signature: _____

Date: _____

Yvonne Savona Ventura
yvonne.savona-ventura.14@um.edu.mt

Prof Lilian M Azzopardi
lilian.m.azzopardi@um.edu.mt

Formola tal-Kunsens tal-Parteċipant/a:

Jiena, hawn taħt iffirmat/a, nagħti l-kunsens tiegħi li nieħu sehem fl-istudju ta' Yvonne Savona Ventura. Din il-formola tal-kunsens tispjega t-termini tas-sehem tiegħi f'din ir-riċerka.

1. Ingħatajt l-informazzjoni bil-miktub u/jew bil-fomm dwar l-iskop tar-riċerka; kelli l-opportunità nagħmel il-mistoqsijiet, u kull mistoqsija ngħatajt tweġiba għaliha b'mod sħiħ u sodisfaċenti.
2. Nifhem ukoll li jiena liberu/a li naċċetta li nieħu sehem, jew li nirrifjuta, jew li nwaqqaf il-parteċipazzjoni tiegħi meta nixtieq mingħajr ma nagħti spjegazzjoni jew mingħajr ma niġi penalizzat/a. Jekk nagħżel li nipparteċipa, jaf niddeċiedi li ma nweġibx kull mistoqsija li ssirli. F'każ li nagħżel li ma nkomplix nieħu sehem fl-istudju, l-informazzjoni li tkun laħqet inġabret mingħandi titħassar dment li jkun teknikament possibbli (ngħidu aħna, qabel ma tiġi anonimizzata jew ippubblikata), u sakemm l-għanijiet tar-riċerka jkunu jistgħu jintlaħqu u ma jintlaqtux serjament. F'dak il-każ, l-informazzjoni tiegħi tintuża u tinżamm anonima.
3. Nifhem li ġejt mistieden/mistiedna nipparteċipa f' kwestjonarju u l-persuna li qed tagħmel ir-riċerka se tigbor informazzjoni rigward l-uzu tiegħi tal- *benzodiazepines* biex tanalizza l-użu ta din il-medicina f'Malta. Jiena konxju/a li il-kwestjonarju se jdum bejn wieħed u ieħor 10 minuti. Nifhem li l-kwestjonarju se jsir f'post u f'ħin li huma komdi għalija.
4. Nifhem li l-parteċipazzjoni tiegħi ma fiha l-ebda riskju magħruf jew mistenni.

5. Nifhem li bil-parteċipazzjoni tiegħi f'dan l-istudju, m'hemm l-ebda benefiċċju dirett għalija. Nifhem ukoll li din ir-riċerka jaf tkun ta' benefiċċju għall-oħrajn għax: iservi bħala qafas biex tinbena protokoll, biex tiggwida lill-prattikanti fl-użu fit-tul tal-*benzodiazepines*.
6. Nifhem li, skont ir-Regolament Ġenerali dwar il-Protezzjoni tad-Data (GDPR) u l-leġiżlazzjoni nazzjonali, għandi dritt naċċessa, nikkoreġi u, fejn hu applikabbli, nitlob li l-informazzjoni li tikkonċernani titħassar.
7. Nifhem li l-informazzjoni kollha miġbura se tinżamm b'mod anonimu meta jintemm l-istudju.
8. Ingħatajt kopja tal-ittra ta' tagħrif biex inżommha u nifhem li se ningħata wkoll kopja ta' din il-formola tal-kunsens.
9. Jiena konxju li d-diskussjonijiet tal-*focus groups* għandhom jitqiesu kunfidenzjali u li m'għandix niżvela dettalji ta' dawk li qed jipparteċipaw u/jew tan-natura tad-diskussjonijiet lil ħaddieħor.

Qrajt u fhimt l-istqarrijiet t'hawn fuq, u naqbel li nipparteċipa f'dan l-istudju.

Isem il-parteċipant/a: _____

Firma: _____

Data: _____

Yvonne Savona Ventura
yvonne.savona-ventura.14@um.edu.mt

Prof Lilian M Azzopardi
lilian.m.azzopardi@um.edu.mt

Focus group participants consent form:

I, the undersigned, give my consent to take part in the study conducted by Yvonne Savona Ventura, under the supervision of Professor Lilian M. Azzopardi and Dr Alison Anastasi. This consent form specifies the terms of my participation in this research study.

1. I have been given written and/or verbal information about the purpose of the study; I have had the opportunity to ask questions and any questions that I had were answered fully and to my satisfaction.

2. I also understand that I am free to accept to participate, or to refuse or stop participation at any time without giving any reason and without any penalty. Should I choose to participate, I may choose to decline to answer any questions asked. In the event that I choose to withdraw from the study, any data collected from me will be erased.

3. I understand that I have been invited to participate in a focus group in which the researcher will ask a set of questions regarding long-term use of benzodiazepines in order to initiate a discussion between the focus group participants. This will be done to develop a framework. I am aware that the focus group will take approximately one hour.

4. I understand that the focus group is to be conducted in a place and at a time that is convenient for me.

5. I understand that my participation does not entail any known or anticipated risks.

6. I understand that there are no direct benefits to me from participating in this study.

7. I understand that, under the General Data Protection Regulation (GDPR) and national legislation, I have the right to access, rectify, and where applicable, ask for the data concerning me to be erased.

8. I understand that all data collected will be stored in a pseudonymised form on completion of the study.

9. I have been provided with a copy of the information letter and understand that I will also be given a copy of this consent form.

10. I am aware that, if I give my consent, the focus group discussion will be audio recorded and transcribed.

11. I am aware that, if I give my consent, extracts from the discussion may be reproduced in these outputs using a pseudonym.

12. I am aware that focus group discussions should be considered confidential and that I should not disclose details of those participating and/or of the nature of discussions to others.

13. I am aware that, if I give my consent, my identity may be revealed in publications, reports or presentations arising from this research, and responses I provide may be quoted directly or indirectly.

14. I am aware that I may ask to be given the opportunity to review relevant extracts of the transcript of my discussion dialogue before the results of the study are published. I am also aware that I may ask for changes to be made if I consider this to be necessary.

I have read and understood the above statements and agree to participate in this study.

Name of participant:_____

Signature: _____

Date: _____

Appendix II:

Data Collection Tool

Data collection tool: Benzodiazepine Use in the Community (English/Maltese):

Questionnaire intended for patients making use of benzodiazepines in the community setting, to be conducted by interview-style.

1. What is your age?

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2. What is your gender?

- ☐ Male
- ☐ Female
- ☐ Prefers not to say

3. Benzodiazepine prescribed:

- ☐ Alprazolam
- ☐ Bromazepam
- ☐ Clonazepam
- ☐ Diazepam
- ☐ Lorazepam
- ☐ Mexazolam
- ☐ Nitrazepam
- ☐ Other: _____

4. What is your prescribed dose?

---

5. Do you follow this prescription?

- ☐ Yes (go to question 7)
- ☐ No (go to question 6)

6. Specify your regimen

---

7. For which diagnosed condition are you being treated?

- ☐ Anxiety
- ☐ Depression
- ☐ Insomnia
- ☐ Psychosis
- ☐ Other: _____

8. How long have you been on a benzodiazepine?

- ☐ Less than 12 months
- ☐ 1 to 3 years
- ☐ 4 to 6 years
- ☐ 7 to 10 years
- ☐ More than 10 years

9. Who originally prescribed the medication?

- ☐ Psychiatrist
- ☐ Family doctor
- ☐ Other: _____

10. How long has it been since you visited that doctor?

- ☐ Less than 12 months
- ☐ 1 to 3 years
- ☐ 4 to 6 years
- ☐ 7 to 10 years
- ☐ More than 10 years

11. List any concurrent medication (psychiatric related only):

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12. Patient is getting medication through:

- ☐ Emergency prescription
- ☐ Control card

13. Locality where questionnaire was conducted:

L-Uzu tal- *Benzodiazepine* fil-Komunita

Kwestjonarju maħsub għal pazjenti li jagħmlu użu minn benzodiazepines fil-komunita, li għandu jsir fis-stil ta' intervista.

Kemm għandek żmien?

X'inhu is-sess tiegħek?

- ☐ Ragel
- ☐ Mara
- ☐ Tippreferi li ma tgħidx

Liem *benzodiazepine* tieħu?

- ☐ Alprazolam
- ☐ Bromazepam
- ☐ Clonazepam
- ☐ Diazepam
- ☐ Mexazolam
- ☐ Nitrazepam
- ☐ Oħrajn:_____

X'inhi id-doża preskritta tiegħek?

Issegwi din ir-riċetta?

☐ Iva (mur għall-mistoqsija 7)

☐ Le (mur għall-mistoqsija 6)

Speċifika id-doża li tieħu

Għal liema kundizzjoni qed tiġi kkurat?

☐ Ansjeta

☐ Depressjoni

☐ Nuqqas ta 'rqad

☐ Psikożi

☐ Raġunijiet oħra:_____

Kemm ilek tieħu l-mediċina?

☐ Inqas minn 12-il xhar

☐ 1 sa 3 snin

☐ 4 sa 6 snin

☐ 7 sa 10 snin

☐ Aktar minn 10 snin

Min oriġinarjament ordna l-medikazzjoni?

☐ Psikjatra

☐ Tabib tal-familja

☐ Tabib iehor: _____

Kemm ilu li kellek appuntament għand dan it-tabib?

☐ Inqas minn 12-il xhar

☐ 1 sa 3 snin

☐ 4 sa 6 snin

☐ 7 sa 10 snin

☐ Aktar minn 10 snin

Elenka kwalunkwe medikazzjoni li qed tieħu (relatata ma psikjatrija biss)

Il-pazjent qed jieħu l-medikazzjoni permezz ta':

☐ Riċetta urgenti

☐ Bil-*control card*

Lokalita fejn sar il-kwestjonarju:
